Summary Table of Study Protocol

Title	Getting to an imprOved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia management (GOULD): a Registry of High Cardiovascular Risk Subjects in the United States
Protocol version identifier	20150230
Date of last version of the protocol	NA
EU Post Authorization Study (PAS) Register No.	To be confirmed
Active Substance	This is a registry of lipid lowering treatment
Medicinal Product	Repatha®
Product Reference	NA
Procedure Number	NA
Marketing Authorization Holder(s)	Amgen
Joint PASS	Is this study conducted with another MAH? No

Research Question and Objectives	**Primary Objective:** • Describe low-density lipoprotein (LDL) treatment patterns over time in subjects with clinical atherosclerotic cardiovascular disease (ASCVD) **Secondary Objectives:** • Describe (LDL-C) levels and measurement patterns in subjects with clinical ASCVD • Describe subject characteristics • Describe subject understanding of CV risk, goals of lipid management and attitudes towards lipid lowering treatment (LLT) **Exploratory Objectives:** • Estimate the effect of subject, physician, and site factors on LLT patterns • Describe management of statin intolerance • Describe changes in LLT patterns after the release of updated lipid management guidelines and/or new clinical study data

Country of Study	United States (US)
Author	

Marketing Authorisation Holder

Marketing authorization holder(s)	NA
MAH Contact	NA

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Investigator's Agreement

I have read the attached protocol entitled "Getting to an imprOved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia management (GOULD): a Registry of High Cardiovascular Risk Subjects in the United States", dated 09 AUGUST2016, and agree to abide by all provisions set forth therein.

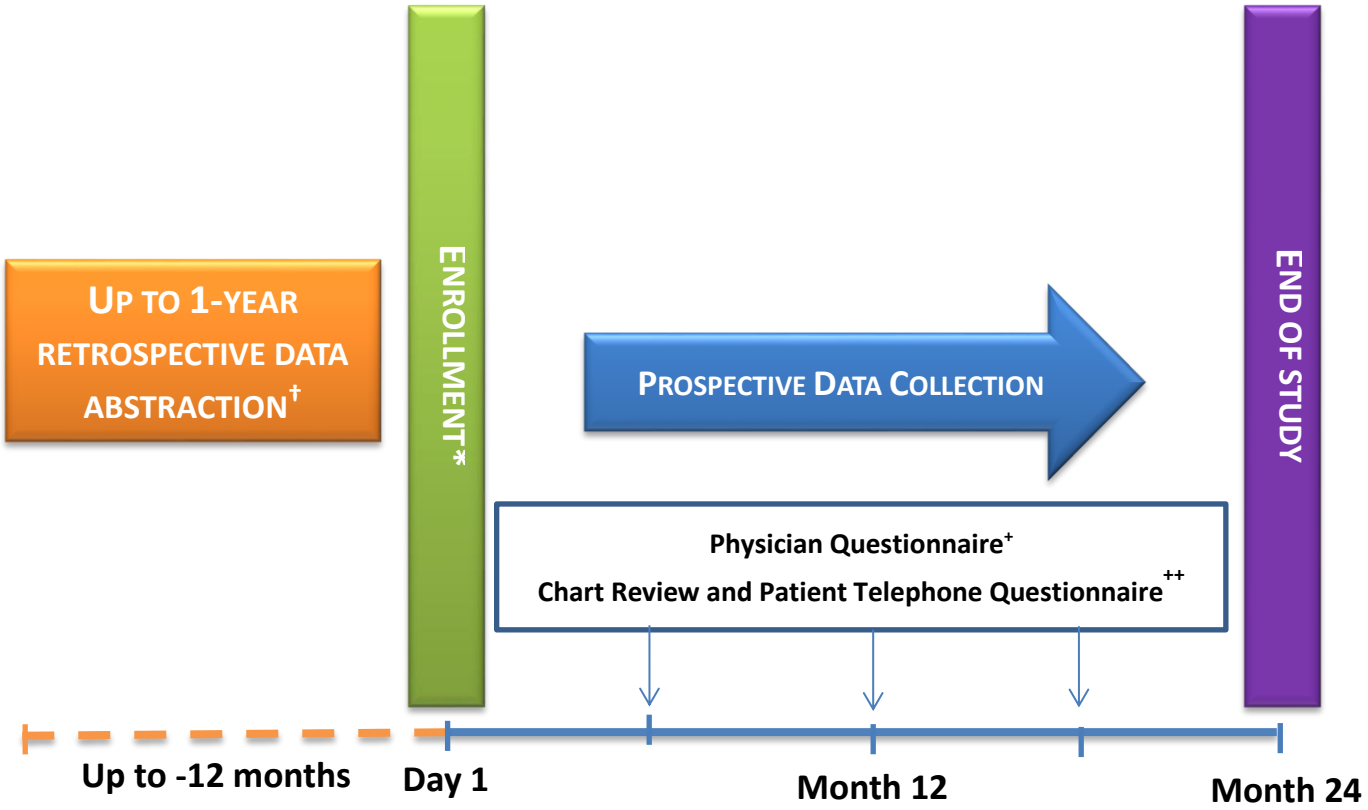
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator

Date (DD Month YYYY)

Study Design Schema



†Data abstraction will be conducted after the patient is confirmed eligible and is enrolled in the study.
*Confirm eligibility criteria
+ After first subject enrolled, Month 12, Month 24
++ Every 6 months

Table 1. Schedule of Assessments

Procedures[a]		Enrollment	Every 6 Months
	Physician	Subject	Subject
Eligibility criteria		X	
Informed consent[b]		X	
Demographics		X	
Chart review[c]		X	X
Weight and height		X	X
Vitals		X	X
Relevant medical/surgical history[d]		X	X
Cholesterol lowering medications		X	X
Concomitant medications		X	X
Relevant clinical laboratory results[e]		X	X
Clinical events[f]		X	X
Medical and drug insurance		X	X
Safety data collection/reporting	X	X	X
Site characteristics[g]	X		
Physician questionnaire on general views of LLT[h]	X		
Subject Telephone Questionnaire[i]		X	X

LLT = lipid lowering treatment; HDL-C=high density lipoprotein cholesterol

a. It is expected that data abstraction and entry into the electronic data capture (EDC) will be conducted at the investigational site.
b. Informed consent must be obtained before any study procedures are performed or initiation of data collection; subjects may be screened to determine if they meet eligibility criteria prior to informed consent.
c. Up to 1-year of retrospective data abstraction from the chart as available to capture the following information as listed here and defined below: relevant surgical/medical history; cholesterol lowering medications; concomitant medications; relevant clinical laboratory results; clinical events; and safety data collection and reporting. Also, chart reviews will occur every 6 months during the prospective period of the study.
d. For medical history specific to cardiovascular (CV) disease, details of diagnostic and therapeutic procedures and their findings will be collected from the chart. Examples include degree of ischemic burden, coronary and peripheral anatomy and degree of stenosis, details of bypass surgery and percutaneous interventions, etc.
e. Data abstraction of available laboratory results that may include low-density lipoprotein cholesterol (LDL-C), triglycerides, HDL-C, and total cholesterol.
f. Clinical events may include myocardial infarction, stroke or transient ischemic attack, hospitalization for unstable angina or heart failure and coronary revascularization.
g. Collected once at study initiation.
h. Physician questionnaires on general view of LLT will occur after enrollment of the first subject and 12 and 24 months thereafter.
i. Subject telephone questionnaires will occur every 6 months.

1. Table of Contents

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2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
ACC/AHA	American College of Cardiology/American Heart Association
ADR	adverse Drug Reaction
ASCVD	atherosclerotic cardiovascular disease
BAS	bile acid sequestrants
BMI	body mass index
CATI	computer-assisted telephone interview
CHD	coronary heart disease
CRF	case report form
CTT	cholesterol Treatment Trialists'
CV	cardiovascular
CVD	cardiovascular disease
eCRF	electronic case report form
EDC	electronic data capture
EMR	electronic medical record
Enrollment	Subject is considered enrolled when informed consent has occurred, eligibility has been determined and data entry initiated into the eCRF.
GOULD	getting to an imprOved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia management
ICH GCP	International Committee for Harmonisation Good Clinical Practice
ICJME	International Committee of Medical Journal Editors
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LDL	low-density lipoprotein
LDLC	low-density lipoprotein cholesterol
LLT	lipid lowering treatment
PCSK9i	proprotein convertase subtilisin/kexin type 9 inhibitor
SADR	serious Adverse Drug Reaction
SEC	self-evident correction
US	United States

3. Responsible Parties

Appropriate sites will be identified, initiated, and contracted. This study will be performed only in the United States (US).

4. Abstract

Study Title: Getting to an imprOved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia management (GOULD): a Registry of High Cardiovascular Risk Subjects in the United States.

4.1 Study Background and Rationale

In subjects with dyslipidemia and clinical atherosclerotic cardiovascular disease (ASCVD), low-density lipoprotein cholesterol (LDL-C) lowering through multiple agents has been shown to reduce the risk of cardiovascular (CV) events (Grundy et al, 2004, Catapano et al, 2011, Stone et al, 2014, Cannon et al, 2015). With the approval of proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i), which reduce LDL-C levels by approximately 60% on top of background lipid lowering treatment, more subjects with ASCVD may be able to achieve lower LDL-C levels, including those with statin intolerance who are unable to tolerate any statins or the higher doses necessary to achieve current LDL-C goals, primarily because of muscle-related side effects (Bruckert et al, 2005).

The landscape of lipid management is rapidly changing and recent observational studies have shown gaps between real-world clinical practice patterns in the United States (US) and guideline-based recommendations to improve lipid management of subjects at high CV risk (Aronow et al, 2010, Athyros et al, 2010, Simpson et al, 2013). The reasons for subjects with coronary heart disease (CHD) not achieving recommended LDL-C levels include failure by both physicians and subjects in following guidelines and treatment recommendations, respectively (Rosenson et al, 2015, Unni et al, 2015).

With the results of large PCSK9i CV outcome studies as well as updates to cholesterol guidelines that are anticipated in 2017, we are in a period of a dynamic, changing landscape. This provides a unique opportunity to study the evolving treatment of hypercholesterolemia by careful observation of subjects with ASCVD receiving care within multiple settings in the US.

4.2 Research Question and Objective(s)

4.2.1 Primary Objective(s)

- Describe low-density lipoprotein (LDL) treatment patterns over time in subjects with clinical ASCVD

4.2.2 Secondary Objectives

- Describe LDL-C levels and measurement patterns in subjects with clinical ASCVD
- Describe subject characteristics
- Describe subject understanding of CV risk, goals of lipid management and attitudes towards lipid lowering treatment (LLT)

4.2.3 Exploratory Objectives

- Estimate the effect of subject, physician, and site factors on LLT patterns
- Describe management of statin intolerance
- Describe changes in LLT patterns after the release of updated lipid management guidelines and/or new clinical study data

4.3 Study Design/Type

This is a multicenter observational cohort study with both retrospective and prospective data collection components in subjects with ASCVD.

4.4 Study Population or Data Resource

The study population will include subjects with ASCVD in the US.

4.5 Summary of Subject Eligibility Criteria

Subjects with ASCVD who may be considered for LLT and who are willing and able to provide informed consent will be eligible for enrollment. The subject population will be recruited into cohorts as follows: approximately 500 subjects on a PCSK9i; approximately 2500 subjects with LDL-C between 70 to 99 mg/dL; and approximately 2000 subjects with LDL-C ≥ 100 mg/dL. All subjects may or may not be currently receiving statins and other LLT. All lipid lowering treatment is at the discretion of the treating physician.

4.6 Follow-up

Physicians will fill out a questionnaire on their general use of LLT at 0, 12, and 24 months following enrollment of their first subject.

Subject charts will be reviewed every 6 months and data will be abstracted for 24 months from the time of enrollment (refer to

Table 1).

In addition, questionnaires will be administered to subjects at 0, 6, 12, 18, and 24 months via computer-assisted telephone interview (CATI) to determine general perceptions and attitudes towards LLT.

4.6.1 Outcome Variables

Primary

- changes in LLT
- initiating or discontinuing statin therapy
- increasing or decreasing the dose of a statin
- switching to a different statin
- initiating or discontinuing ezetimibe
- initiating or discontinuing a PCSK9i
- increasing or decreasing the dose of a PCSK9i
- switching to a different PCSK9i
- change in other LLT (defined as bile acid sequestrants [BAS], prescription LLT, mipomersen, lomitapide, apheresis, and any new LLT therapy that enters the market after study initiation)
- no change in LLT

Secondary and Exploratory

- whether or not LDL-C (mg/ dL) and other lipid values are measured, and if so, date and value (mg/dL)
- physician-level questionnaire
    - physician lipid treatment objective in subjects with ASCVD
        - lower LDL-C
        - manage other lipid parameters
        - treating subjects with any dose of statin therapy

        - treating subjects with maximally tolerated statin therapy
        - reduce CV risk
        - other
- subject -level Questionnaire
    - subject reported outcomes
        - baseline characteristics (at enrollment)
        - reported LLT
        - general Perceptions and attitudes towards LLT

4.6.2 Exposure Variables

Not applicable

4.6.3 Covariate(s)

- subject characteristics
- prior history of CV events qualifying subject for enrollment
- physician characteristics
- site characteristics

4.7 Study Sample Size

With 5000 subjects (all enrolled subjects), the percentage of subjects with a given LLT pattern (eg, adding a non-statin therapy, reducing a statin dose, or switching statins) would be estimated with a 95% confidence interval no wider than +/- 0.69%. For analysis limited to a 2000 subject cohort, the maximum confidence interval would be +/-1.10%.

4.8 Data Analysis

Analyses will be performed both at subject level and at the physician level. Continuous variables will be summarized by a mean, median, standard deviation, standard error, quartiles, minimum and maximum. Categorical variables will be summarized by number and percentage. Point estimates of outcomes will be accompanied by 95% confidence intervals.

5. Amendments and Updates

None.

6.

Periodic data analyses will be conducted throughout study period.

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Dyslipidemia and, specifically, high concentrations of LDL-C are at the core of atherosclerotic plaque formation and the development of cardiovascular disease (CVD). LDL-C lowering through multiple agents – statins, and more recently ezetimibe – has been shown to reduce the risk of CV events, and practice guidelines universally recommend LDL-C reduction in high-risk subjects (Grundy et al, 2004; Catapano et al, 2011; Stone et al, 2014). Further support of LDL-C reduction is corroborated by the large meta-analysis by the Cholesterol Treatment Trialists' (CTT) Collaboration, which included 26 randomized controlled studies involving nearly 170,000 hyperlipidemic subjects treated with statins, and demonstrated that for every 1 mmol/L (39 mg/dL) reduction in LDL-C, there was a 20% reduction in the risk of CVD events (CTT, 2010).

7.1.1 Treatment Gap between Clinical Practice and Guidelines/Recommendations

Although LDL-C reduction has improved over the years with use of high-intensity statins, between 70 to 80% of subjects in certain high-risk groups (eg, diabetics with CHD, individuals with heterozygous familial hypercholesterolemia) do not reach recommended lipid targets; indeed, in the broader ASCVD population only about one third of high-risk subjects reach an LDL-C < 70 mg/dL over time (Waters et al, 2009). Moreover, recent evidence suggests high-risk subjects are not only switched from high- to low- or intermediate-

dose statins, but also many subjects discontinue their statins altogether, which raises LDL-C levels and increases the risk of CV events. Detailed information on the reasons for sub-optimal lipid management is lacking; however, several factors are hypothesized to play a role. These include physician preferences, education, therapeutic drug costs and access, and subject factors including demographics, subject preferences, medication adherence, and potential drug interactions (Kim et al, 2003, Atar et al, 2009, Athyros et al, 2010, Toth, 2014).

A number of recent observational studies have shown gaps between real-world clinical practice patterns in the United States (US) and guideline-based recommendations to improve lipid management of subjects at high CV risk. A 2013 publication from a large managed care setting showed that subjects at high CV risk were frequently initiated on medium-intensity statins and were not up-titrated, as recommended by guidelines, and that nearly half of the subjects discontinued lipid lowering treatment (LLT) by the end of 1 year (Simpson et al, 2013). This practice of initiating low dose or medium dose statins for high risk subjects has been reported in other observational studies (Aronow et al, 2010; Athyros et al, 2010). Additionally concerning is that a large number of Medicare beneficiaries do not fill their prescriptions for high intensity statins following hospitalization for CHD, as recommended by the 2013 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (Rosenson et al, 2015). Similar observations have been noted in a 2015 publication using a large claims research database where subjects with CHD and CHD risk factors, eg, diabetes, peripheral vascular disease, stroke – were identified, and it was noted that even though statin use increased over time, most subjects were prescribed moderate intensity statins, and nearly 40% of subjects were not getting statin prescriptions at 1 year of follow up (Unni et al, 2015).

7.1.2 The Changing United States Landscape in Lipid management

Data from the Improved Reduction of Outcomes: Vytorin Efficacy International Trial demonstrated that further lowering of LDL-C with a non-statin lipid lowering agent (ezetimibe), when added to statin therapy, reduced CV events (Cannon et al, 2015). This study demonstrated that additional non-statin lipid lowering to approximately 53 mg/dL, well below 70 mg/dL, a target LDL-C value from the modified Adult Treatment Pattern III guidelines for very high-risk subjects – further lowered CV events, suggesting that lower LDL-C

continues to confer CV benefit. With the approval of PCSK9i, have reduced LDL-C levels by approximately 60% on top of background lipid lowering treatment in clinical studies, more subjects with high CV risk may be able to achieve lower LDL-C levels.

Recently, American College of Cardiology published the expert consensus decision pathway on the role of non-statin therapies in the management of atherosclerotic CV risk and suggests place-in therapy for non-statins and recommends PCSK9 inhibitors as second line non-statin therapy in addition to ezetimibe for ASCVD subjects. In subjects with LDL-C ≥ 190 mg/dL, either ezetimibe or PCSK9i can be considered after statins. The recommended LDL-C thresholds for the addition of ezetimibe or PCSK9 inhibitors vary according to the population:

- ≥ 70 mg/dL for ASCVD subjects with comorbidities
- ≥ 100 mg/dL for ASCVD without comorbidities or LDL ≥ 190 mg/dL with ASCVD risk factors
- ≥ 130 mg/dL without ASCVD risk factors

During 2017, the results of large CV outcomes studies with PCSK9i are expected to report out, which could lead to updates to cholesterol lowering guidelines. Hence, we are in a period of a dynamic, changing landscape, characterized by new treatment options, new data, and potentially evolving guidelines. This rapidly changing landscape provides a unique opportunity to observe the evolving treatment of hypercholesterolemia, and the Getting to an imprOved Understanding of Low-Density Lipoprotein Cholesterol and Dyslipidemia management (GOULD) study is designed to do so via careful observation of subjects with ASCVD receiving care within multiple settings in the US.

7.2 Rationale

The purpose of this study is to better understand cholesterol treatment patterns in the context of a changing landscape in subjects with ASCVD. We are particularly interested in ASCVD subjects that may be undertreated, including those who have indications for intensification of statin treatment, or have indications to consider add-on therapy to statins. In addition to these subjects, we are also interested in subjects with statin intolerance that are unable to tolerate any statins or the higher doses necessary to achieve current LDL-C goals, primarily because of muscle-related side effects (Bruckert et al, 2005).

This observational registry of ASCVD subjects will provide:

- Prospective, granular, subject level information and hypercholesterolemia treatment patterns in real-world clinical practice at various enrolled sites representing multiple care delivery settings
- Assessment of factors that may influence physician's treatment decisions
- An understanding of reasons for non-statin therapy initiation (including PCSK9i)
- An understanding of the challenges of initiation of non-statin therapy

7.3 Statistical Inference (Estimation or Hypothesis)

No formal hypothesis will be tested in this observational study. Point estimates of outcomes (eg, the percent of subjects intensifying non-statin therapy) will be generated along with 95% confidence intervals.

8. Research Question and Objectives

8.1 Primary Objective

- Describe LDL treatment patterns over time in subjects with clinical ASCVD

8.2 Secondary Objectives

- Describe LDL-C levels and measurement patterns in subjects with clinical ASCVD
- Describe subject characteristics
- Describe subject understanding of CV risk, goals of lipid management and attitudes towards LLT

8.3 Exploratory Objectives

- Estimate the effect of subject, physician, and site factors on LLT patterns
- Describe management of statin intolerance
- Describe changes in LLT patterns after the release of updated lipid management guidelines and/or new clinical study data

9. Research Methods

9.1 Study Design

This is a prospective multicenter observational cohort study with retrospective component/chart review of ASCVD subjects that is designed to describe practice patterns of cholesterol management in such subjects in the US.

Up to 1 year of retrospective lipid treatment, lipid measurement patterns, and CV data in subjects with ASCVD meeting inclusion/exclusion criteria at enrolled clinical sites will be captured. The retrospective data collection is being performed for the following reasons:

- Capture relevant factors related to subject's CV risk and pertinent medical history
- Capture changes in LLT over time as related to the subject's clinical condition and medical history and adverse events to LLT

Eligible subjects will be invited to enroll in chronological order of attending the clinic.

The study will enroll 3 subject cohorts with the following rationale:

1) the first cohort will consist of approximately 500 subjects on PCSK9i at the time of enrollment. The goal is to include a large enough cohort of patients receiving PCSK9i in real world clinical practice; this will allow (for the first time) to better understand the characteristics of those patients whose treatment is escalated to include PCSK9i, the therapeutic effects of PCSK9i outside of the randomized clinical trial settings, and over a prolonged duration of follow up;

2) the second cohort will enroll approximately 2000 subjects with LDL-C levels ≥100 mg/dL. The purpose is to include a large group of patients with established ASCVD and suboptimal LDL control – to better understand the treatment patterns and rates of CV events in this group;

3) the third group will enroll approximately 2500 subjects with LDL-C levels between 70 and 99 mg/dL. The purpose is to include a large group of patients with established ASCVD and more optimal control of LDL – to better understand patient characteristics, lipid-lowering treatment management, rates of CV events, and potential opportunities for further LLT optimization in this group.

Interactive voice response system will be used to track the number of subjects in each cohort. Once a cohort is filled, no more subjects may be enrolled into it.

After the first subject is enrolled and annually thereafter, physicians will fill out a questionnaire on their general use of LLT type and dose and their overall goals of lipid management.

The study specific data collection points are aligned with the standard of care physician scheduled visits. Each subject will be followed through a systematic series of medical chart reviews conducted at participating clinical sites. Initial chart reviews will occur at subject enrollment with subsequent scanning of charts occurring at the site every 6 months thereafter.

In addition, questionnaires will be administered to subjects every 6 months via a CATI system (wherein an interviewer will ask the subject a series of standard questions) to determine general perceptions and attitudes towards LLT. The order of questions in the questionnaire will be based on subject response. This will facilitate reports of the number of inpatient visits, outpatient visits, outpatient procedures, diagnostic tests, prescription and nonprescription medication use in the prior 6 months. Subjects will be asked to complete questionnaires even if they do not routinely see the enrolling physician or if they have switched providers.

9.2 Setting and Study Population

9.2.1 Study Period

The estimated duration of this study is approximately 30 to 36 months which includes an estimated 6 to 12 month enrollment period. Each subject will be followed prospectively for 24 months from the time of enrollment.

9.2.2 Selection and Number of Sites

Centers that treat at least 40 ASCVD subjects for hypercholesterolemia per month will be eligible for participation in this study. It is estimated that a selection of approximately 120 enrolling sites will be required to achieve a target of 5000 subjects in this study. Sites that do not enroll any subject in the first 3 months may be closed.

9.2.3 Subject Eligibility

9.2.3.1 Inclusion Criteria

Subject

- ≥ 18 years of age at signing of informed consent
- at least 1 planned visit in the next 12 months
- available for follow-up questionnaires
- established ASCVD defined as meeting at least 1 of the following criteria:
    - coronary artery disease
    - prior history of myocardial infarction
    - coronary or other arterial revascularization
    - ischemic stroke or transient ischemic attack
    - documented peripheral arterial disease secondary to atherosclerosis (., aortic aneurysm, ankle brachial index < 0.9, imaging evidence of > 50% stenosis in any peripheral artery, or intermittent claudication)
    - carotid artery stenosis

Cohorts

- For the cohort of approximately 500 subjects taking a PCSK9i at baseline: evidence of a current prescription for an approved PCSK9i and subject confirmation that they have taken a PCSK9i within 30 days prior to enrollment
- For the cohort of approximately 2000 subjects with LDL-C ≥ 100 mg/dL at last measurement: confirmation of LDL-C ≥100 mg/dL with no change in LLT for 4 weeks (statin and other non-statin therapies). For the cohort of approximately 2500 subjects with LDL-C 70-99 mg/dL at last measurement: confirmation of LDL-C 70-99 mg/dL with no change in LLT for 4 weeks

9.2.3.2 Exclusion Criteria

Subject

- Unable or unwilling to provide informed consent including but not limited to cognitive or language barriers
- Current or planned participation in an interventional clinical study involving any investigational medical device or drug treatment at the time of enrollment
- Life expectancy <12 months
- Currently pregnant, breast feeding, or planning to become pregnant*

*While subjects that are pregnant are not eligible for the study, if a site investigator has a subject that becomes pregnant while receiving evolocumab, they will be advised to refer the subject to Amgen's evolocumab pregnancy registry (study #20150338, *Evolocumab Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study*) *(*for contact information, refer to Section 11.2 pertaining to Amgen's evolocumab pregnancy registry*)*

9.2.4 Matching

Not applicable.

9.2.5 Retrospective Period

The Retrospective Period is the time prior to enrollment when data will be extracted from subjects' charts for up to 1 year prior. Data extracted will include listings in

Table 1.

9.2.6 Baseline (Enrollment) Visit

A subject questionnaire will be obtained at enrollment.

Data captured from a review of the subject's chart at the time of the enrollment visit will include demographics, comorbidities, all disease characteristics, and LLT. See

Table 1 for schedule of assessments.

9.2.7 Prospective Period

Once subjects are enrolled and retrospective data are obtained, data will be collected from subject encounters at the clinic (

Table 1) for 24 months.

Each subject will be followed through a systematic series of medical chart reviews conducted at participating clinical sites. Chart reviews will occur every 6 months after enrollment. If there was a subject encounter (eg, subject seen at the site, subject contacted by telephone) within the previous 6 months, data will be abstracted from the chart. Subjects included in the study will continue to have data from their medical chart abstracted until the first occurrence of the following events: subject withdraws consent, subject is lost to follow-up, subject dies, or the subject completes the 24-month study. In addition, questionnaires will be administered to study participants every 6 months via CATI. Physicians will fill out an annual questionnaire on their general use of LLT type and dose and their overall goals of lipid management.

9.3 Variables

9.3.1 Exposure Assessment

Not applicable.

9.3.2 Outcome Assessment

Primary

- changes in LLT
- initiating or discontinuing statin therapy
- increasing or decreasing the dose of a statin
- switching to a different statin
- initiating or discontinuing ezetimibe
- initiating or discontinuing a PCSK9i
- increasing or decreasing the dose of a PCSK9i
- switching to a different PCSK9i
- change in other LLT (defined as BAS, prescription LLT, mipomersen, lomitapide, apheresis, and any new LLT therapy that enters the market after study initiation)
- no change in LLT

Secondary and Exploratory

- whether or not LDL-C (mg/dL) and other lipid values as measured, and if so, date and value (mg/dL)
- Physician-level Questionnaire
- lipid treatment objective in subjects with ASCVD
    - lower LDL-C

  - manage other lipid parameters
  - treating subjects with any dose of statin therapy
  - treating subjects with maximally tolerated statin therapy
  - reduce CV risk
  - other
- Subject -level Questionnaire
- Subject reported outcomes
  - baseline characteristics (at enrollment)
  - reported LLT
  - general Perceptions and attitudes towards LLT

9.3.3 Covariate Assessment

Covariates in this study are the potential predictors of change in LLT, specifically:

- subject characteristics:
  - demographics
  - cardiovascular history
  - non-CV comorbidities
  - considered to be statin-intolerant
  - concomitant medications
  - insurance status
  - duration of exposure to lipid lowering treatment
  - educational status
  - socioeconomic status
  - financial burden of the current medications
  - marital status
  - attitudes towards medication
  - smoking
  - single event vs. recurrent event vs. other reason for ASCVD diagnosis
  - family history of CVD
  - vital signs
  - Body Mass Index
  - general laboratory data (creatinine clearance and hemoglobin)
- prior history of CV events that qualified subject for study:
  - myocardial infarction
  - stroke or transient ischemic attack
  - hospitalization for unstable angina or heart failure
  - coronary and peripheral vascular revascularization

- physician characteristics:
  - specialty (cardiology, other specialty) vs. primary care
  - years in practice
  - gender
  - general approach to lipid therapy: LDL target vs. percentage lowering vs. drug usage
- site characteristics:
  - geographic region
  - degree of formulary control over the site
  - presence of lipid protocols and frequency of update
  - rural vs. urban
  - electronic medical records vs. paper records
  - academic vs. private practice

9.3.4 Validity and Reliability

Data for this study will be collected via abstraction from a subject's electronic health record (or medical chart) as well as via subject and physician questionnaires. Given that the abstraction will be completed at the site, there may be inter-abstractor differences such that some abstractors are more experienced, thorough, etc. To mitigate this, all abstractors will be trained in how to best abstract electronic health record/chart data into the study-specific electronic case report forms (eCRFs). The call center will use a CATI system such that complicated skip patterns built into the questionnaire are invisible to the interviewer and will reduce the likelihood of errors.

9.4 Data Sources

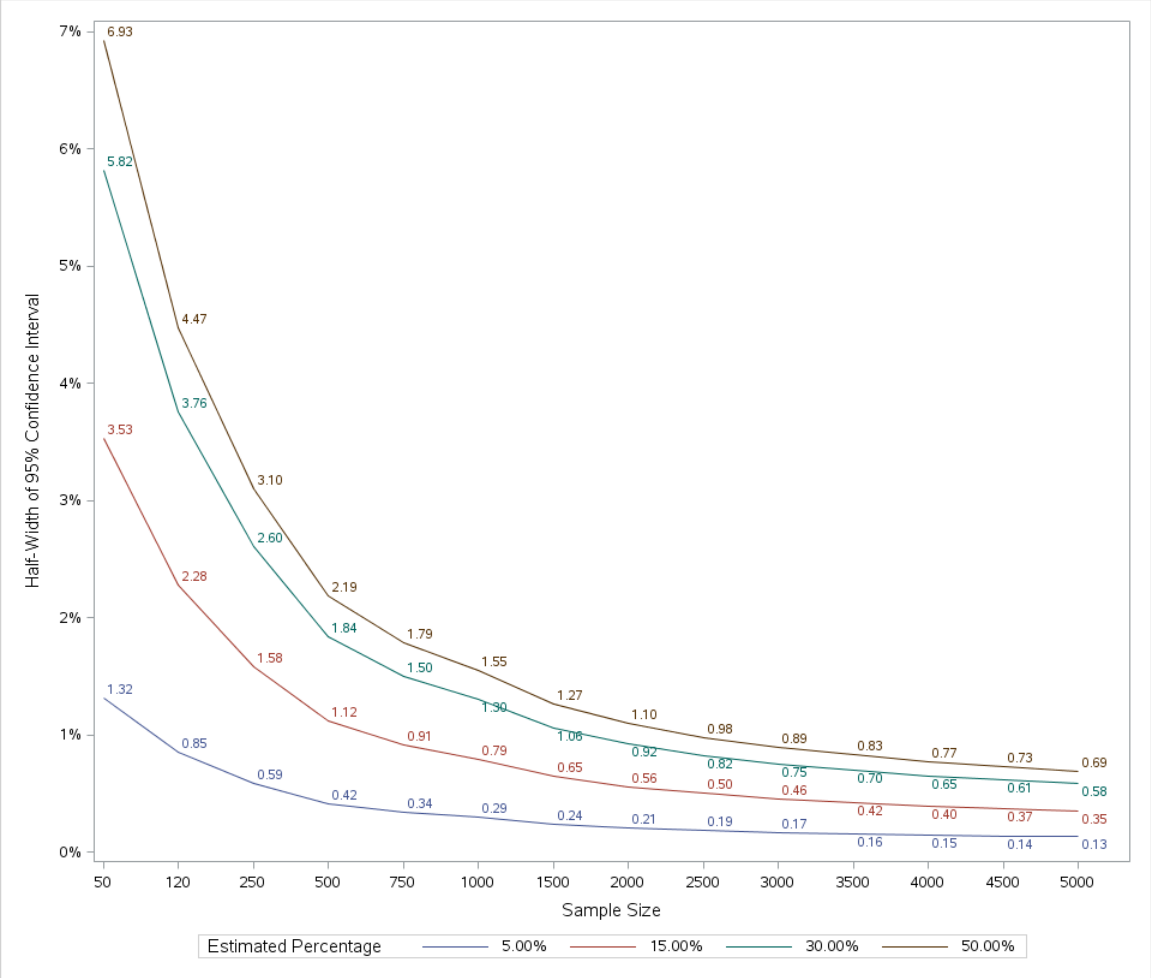
Data will be provided by study site staff, utilizing subject charts to abstract information in order to complete eCRFs in the study-specific electronic database. Data from physician and subject questionnaires will be collected in a database that is separate from that at the sites.

9.5 Study Size

The planned sample size is 5000 subjects total and 120 physicians. **Error! Reference source not found.** shows the estimated half-width of a 95% confidence interval for the percentage of subjects who experience a specific change in LLT (eg, up-titrating statin therapy, adding non-statin therapy) or the percentage of physicians who respond a certain way to a questionnaire item (eg, selecting a certain treatment objective). The margin of error is presented for potential percentages we might observe (ranging from

5% to 50%) and for the various sample sizes in our analyses ranging from 50 (a potential small subject subgroup or larger subgroup of physicians) to 5000 (the total subject sample size). For an analysis on all enrolled subjects, the 95% confidence interval for an LLT change present in 5% of the sample will have a half-width of 0.13%. For an analysis on all enrolled subjects, the 95% confidence interval for an LLT change present in 50% of the sample will have a half-width of 0.69%. For analysis on a 2,000 subject cohort, the half-widths for an LLT change of 5% and 50% would be 0.21% and 1.10%, respectively. For analysis on 120 physicians, the half-width of the 95% confidence interval for a multiple choice question response rate of 5% will be 0.85%. For analysis on 120 physicians, the half-width of the 95% confidence interval for a multiple choice question response rate of 50% would be 4.47%.

Figure 1: Half-Width of 95% Confidence Interval by Sample Size and Estimated Proportion



Half-width of 95% confidence interval for given proportions of the population and group or sub-group sample sizes. Note that the x-axis scale is not linear.

9.6 Data Management

Data are abstracted by site staff from subject charts into an electronic database provided by the Sponsor. Protocol-specific training and eCRF completion instructions will be provided to all site staff delegated to abstract subject data will be provided.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the physician 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 eCRFs 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 eCRFs in accordance with the local laws and regulations.

The physician 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 eCRFs must be maintained and available upon request.
- Updates to eCRFs 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 and/or site notifications are created in the electronic data capture (EDC) system database for site resolution and closed by Amgen reviewer.
- The physician signs only the Physician Verification Form for this EDC study. This signature indicates that the physician inspected or reviewed the data on the eCRF, the data queries, and site notifications, and agrees with the content.
- Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical study database. Self-evident corrections (SCE) will be documented in the Standard SCE document and the eCRF Specific Instructions, both of these will be available through the EDC system. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (ie, the same results sent twice with the same date but different visits) and updating a specific response if the confirming datum is provided in the "other, specify" field (eg, for race, reason for ending study).

9.6.1 Obtaining Data Files

Not applicable.

9.6.2 Linking Data Files

A unique subject enrollment number will link data abstracted from the chart into the CRF with data collected from the subject questionnaire.

9.6.3 Review and Verification of Data Quality

Review and verification of data quality is described in Section 9.6.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Periodic Data Reports

A baseline analysis will be conducted after the last subject is enrolled. Additional data analyses will be conducted on periodic basis throughout study period.

9.7.1.2 Final Analysis

The final analysis will be conducted when data from all subjects and physicians are complete. Subjects will be followed until they die, are lost to follow-up, withdraw consent, or complete 24 months of prospective follow-up, whichever comes first.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

The unit of analysis will be the subject or the physician, depending on the data being summarized. Continuous variables will be summarized by the evaluable sample size, mean, median, standard deviation, standard error, quartiles, minimum and maximum. Categorical variables will be summarized by the evaluable sample size, and the number and percent in each category. Point estimates of key outcomes will be accompanied by 95% confidence intervals.

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 and incomplete information is not expected in this regard.

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

Missing data will be summarized by presenting the number of evaluable subjects for each analysis.

9.7.2.3 Description of Study Enrollment

Subject and physician enrollment will be summarized by cohort (subject summary only), practice type, and geographic region.

9.7.2.4 Description of Subject and Physician Characteristics

Subject, physician, and site characteristics described in Section 9.3.3 will be summarized by the descriptive statistics listed in Section 9.7.2.1; subject level summaries will be provided by cohort and overall.

9.7.2.5 Analysis of the Primary, Secondary and Exploratory Endpoints

9.7.2.5.1 Primary Endpoints

The proportion of subjects with a specific change in LLT as described in Section 9.3.2 (eg, up-titrating statin therapy, adding non-statin therapy such as ezetimibe or a PCSK9i, etc.) will be estimated along with a 95% confidence interval.

9.7.2.5.2 Secondary Endpoints

Low density lipoprotein cholesterol will be summarized by the descriptive statistics listed in Section 9.7.2.1; the mean will be accompanied by a 95% confidence interval. The percent change in LDL-C from select time points will also be summarized.

The proportion of physicians stating a specific lipid treatment objective will be estimated for each objective offered (eg, lower LDL-C, manage other lipid parameters, etc.).

Responses to the subject questionnaire on CV risks, goals of LLT, and attitudes of LLT will be summarized by frequency and percent.

9.7.2.5.3 Exploratory Endpoints

Hierarchical logistical modeling will be employed to describe the relationship of site, physician, and subject predictors of interest on treatment decisions. Data regarding provider definitions of statin intolerance will be collected by way of multiple-choice questionnaire and answers will be summarized by frequency and percent. Subject use of each LLT of interest will be summarized by calendar time to examine potential guideline changes in care during the course of the study.

9.7.3 Sensitivity Analysis

9.7.3.1 Subgroup Analysis

Primary and secondary endpoints will be summarized by subgroups based on select site, physician, and subject characteristics.

Please refer to Section 9.3.3 for details regarding site, physician, and subject characteristics.

9.7.3.2 Stratified Analysis

The analyses will be stratified by cohort. For select endpoints, summaries may be provided across cohorts if relevant (eg, the PCSK9i cohort would not be combined with the other 2 cohorts when summarizing the percentage of subjects initiating a PCSK9i). Caution should be used when interpreting results across cohorts because the cohort-weighted enrollment unique to this study limits the generalizability of a combined cohort estimate. Inverse variance weighting will be used when combining estimates across cohorts and homogeneity across strata will be evaluated.

9.7.3.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

9.7.3.4 Other Sensitivity Analysis

Not applicable.

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

Adverse events will be coded using the current version of the Medical Dictionary for Regulatory Activities and summarized.

9.8 Quality Control

As described in Section 9.6.3 attempts to verify the data will be made by Amgen responsible for verifying the eCRFs for completeness, accuracy, and consistency of the data.

9.9 Limitations of the Research Methods

9.9.1 Internal Validity of Study Design

The internal validity of the study depends upon the quality and completeness of the source data and the integrity of its transfer into the study database through the process of data collection. Measures to be taken to minimize error include careful design of the data collection tool in order to ensure that they are intuitive and user friendly. Errors will be captured by means of edit checks and site queries.

9.9.1.1 Measurement Error(s)/Misclassification(s)

Not applicable.

9.9.1.2 Information Bias

The risk of information bias for this study is considered to below. The data sought from the subject's medical record is routinely recorded information and should be readily

available for capture. For information captured via the physician and subject questionnaires, limitations surrounding self-reported data apply.

There is the possibility of differences in data capture between site-level abstractors, although abstractors will be trained using study-specific eCRFs on methods for abstracting data from the subject's medical record. It is possible that information for more clinically complicated subjects might be recorded with more or less detail than for other subjects, resulting in differential bias, although this is expected to be consistent across sites. Additionally, there may be less reports of non-serious adverse events in the medical chart as compared with serious adverse events. However, it is anticipated that any adverse event resulting in hospitalization will be recorded in the subject's medical chart.

The physician questionnaire administered at baseline and annually thereafter will be designed to be physician friendly and to not take more than 15 to 30 minutes of the physician's time per subject. The questions will center around general attitudes toward the physicians' practices with respect to treating subjects with established ASCVD.

Finally, by employing a centralized call center with trained personnel and CATI technology to administer the subject questionnaire, we will mitigate against additional biases that might result from site-specific administration of the questionnaire.

9.9.1.3 Selection Bias

The study is subject to possible selection bias because the investigational sites and subjects who agree to participate will be determined from:

- Physician /site and subject willingness to participate in the study
- Site personnel's preferences to enroll certain subjects
- Physician /site and study coordinator experience with the conduct of similar studies
- Physicians/sites that may demonstrate a more or less conservative treatment practice as a result of a collection of factors and exposure to factors that impact dyslipidemia treatment practice

The implication of the selection bias is that the results may lack generalizability to practices outside the select group of participating sites. In order to lessen this bias, practices not necessarily extensively involved in clinical research, across the US that are representative of a high proportion of practices treating high CV risk subjects who are candidates for LLT are intended to be enrolled.

To avoid selection bias of subjects at the individual site level, eligible subjects will be invited to enroll in chronological order of attending the clinic. Sites selection will result in a sample set of sites that:

- Are representative of dyslipidemia management across the US
- Have some experience in the conduct of clinical research (but not a strict requirement to avoid introducing bias toward clinical research sites)
- Have a keen interest in the proposed study
- Show, through feasibility, an adequate eligible population to ensure timely subject recruitment for the study

9.9.1.4 Confounding

Estimations of associations or effects are restricted to the exploratory objective. For these analyses, estimations of effects (including potential comparisons across subgroups) will employ appropriate methods to account for possible confounding as needed.

9.9.2 External Validity of Study Design

External validity of this study may be limited. The subject population is restricted to those subjects with a LDL-C ≥70 mg/dL unless on a PCSK9i. The study population is also oversampled with subjects on a PCSK9i. Consequently the population will be skewed to be more representative of subjects on PCSK9is than the general population. In addition the enrollment population is divided into 2 additional cohorts who are meant to be representative of subject types who may be candidates for LLT intensification. Thus, the study population may not reflect that of the general population.

9.9.3 Analysis Limitations

As all estimation analyses will be descriptive in nature, issues related to confounding are not relevant and significant issues related to bias are not expected.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Complete and high quality information for key study variables are anticipated given data will derive from medical chart review. For information captured from the physician questionnaire and subject questionnaire, standard techniques will be used to minimize missing elements.

Methods for handling missing data will be described in further detail in the Statistical Analysis Plan.

10. Protection of Human Subjects

10.1 Informed Consent

Informed consent is required to be obtained before a subject's participation in the study.

An initial sample informed consent form is provided for use at the sites where subjects are treated. The written informed consent document should be prepared in the language(s) of the potential subject participants.

Before a subject's participation in the study, the physician is responsible for obtaining written informed consent from the subject or subject's legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits and potential hazards of the study. A legally authorized representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The physician is also responsible for asking the subject if the subject has a primary care physician, and if the subject agrees to have his/her primary care physician informed of the subject's participation in the study. If the subject agrees to such notification, the physician is to inform the subject's primary care physician of the subject's participation in the study. If the subject does not have a primary care physician and the physician will be acting in that capacity, the physician is to document such in the subject's medical record.

The acquisition of informed consent and the subject'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 authorized representative, the physician 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.
Physician consent will be collected as applicable.

10.2 Institutional Review Board

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or other relevant ethical review board for written approval. A copy of the written approval of the protocol and informed consent/assent form must be received by Amgen before study can be executed.

The physician 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. The physician 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 physician is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval /renewal throughout the duration of the study. Copies of the physician's reports and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

10.3 Subject Confidentiality

The physician 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 eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For safety events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the physician, except as described below.

In compliance with Federal regulations/International Conference on Harmonisation (ICH) GCP Guidelines, it is required that the physician and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study.

The physician 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 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 medicinal product(s), combination product or medical device 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 physician's responsibility to evaluate whether an adverse event is related to an Amgen product (ie, is an adverse drug reaction) 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 Adverse Drug Reaction

An adverse reaction is a response to a pharmaceutical product(s) which is noxious and unintended. This includes adverse reactions which arise from:

- the use of a pharmaceutical product within the terms of the marketing authorisation;
- the use outside the terms of the marketing authorisation, including overdose, off-label use, misuse, abuse and medication errors;
- occupational exposure.

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected pharmaceutical product and an adverse event (See Section 11.1.1 for definition of an adverse event).

An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.

11.1.3 Serious Adverse Events

A serious adverse event is any adverse event as defined above that meets at least 1 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.

11.1.4 Serious Adverse Drug Reaction

A serious adverse drug reaction is a serious adverse event (as described above in Section 11.1.3) with at least a reasonable possibility of a causal relationship between a suspected pharmaceutical product and an adverse event (See Section 11.1.1 above for definition of an adverse event).

11.1.5 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 (for additional information, refer to Section 11.2 pertaining to Amgen’s evolocumab pregnancy registry),
- 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).

11.1.6 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 evolocumab.

11.2 Safety Reporting Requirements

In this study, the collection and reporting of safety information is required for subjects exposed to evolocumab. In the unlikely occurrence of an adverse event, other safety finding and/or product complaint (safety events) being reported with the use of other Amgen products, the event will be treated as a spontaneous report, therefore, the event may be reported spontaneously via the standard spontaneous reporting route.

See Appendix F for a list of Amgen products marketed in the US.

Reporting Safety Events During the Retrospective Period:

The retrospective period is the time prior to enrollment when data will be abstracted from subjects' charts for up to 1 year prior (data abstraction - see Table 1). During this period, retrospective chart review, those safety events (all ADRs, SADRs, product complaints and other safety findings) for subjects exposed to evolocumab will be collected and reported to Amgen. The physician is responsible for ensuring that safety events for subjects exposed to evolocumab must be recorded in the subject's appropriate study Case Report Form (eg. Event CRF) and submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of physician's awareness.

Reporting Safety Events During the Prospective Period:

The physician is responsible for ensuring that safety events (all ADRs, SADRs, product complaints and other safety findings) for patients exposed to evolocumab observed by the physician or reported by the subject that occur after signing of the informed consent form through the final study contact (including safety events reported through the subject

questionnaires), are recorded in the subject's appropriate study Case Report Form (eg. Event CRF). 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 physician's awareness.

Subject questionnaires:

The vendor (eg. centralized call-center) administering the patient questionnaires is responsible for ensuring that safety events (all adverse events: non-serious, serious**,** related, non-related, product complaints and other safety findings) for evolocumab reported by the subject that occur after signing of the informed consent form through the final study contact are reported to the study site within 1 business day of the vendor's awareness. Communication of safety events to the study site will be achieved via an automated email notification that is triggered by information collected. The physician is responsible for recording events in the subject's appropriate study Case Report Form (eg. Event CRF) and performing a causality assessment for all adverse events. The physician is responsible for submitting all ADRs, SADRs, product complaints and other safety findings as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of physician's awareness.

If the EDC system is unavailable to the site staff to report the adverse event, the information is to be reported to Amgen via a paper Adverse Event Contingency Report Form within 1 business day of the physician's awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Adverse Event Contingency Report Form the data must be entered into the EDC system when the system is again available.

See Appendix C for a sample Safety Report Form (eg, Adverse Event Contingency Report 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. While subjects that are pregnant are not eligible for the study, if a site physician has a subject that becomes pregnant while receiving evolocumab, the subject should be referred to Amgen's evolocumab pregnancy registry (study #20150338, *Evolocumab Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study*).

How to contact:

MotherToBaby Pregnancy Studies conducted by the OTIS

Website: http://mothertobaby.org/pregnancy-studies/

Phone:1-877-311-8972

The physician 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

Exempted events are those not considered by the physician to have a causal relationship with evolocumab administration. This observational study is not designed or adequately powered to identify new significant safety information that would change the safety profile of evolocumab established in large interventional clinical trials, including an ongoing ~27,500 subject CV outcomes study. Therefore, only those adverse events considered by the physician to be related to evolocumab (ie, adverse drug reactions) together with other safety findings and product complaints (refer to protocol definitions) will be collected.

If any of the exempted events have a fatal outcome, they should be considered a serious adverse event and must be reported individually within 1 business day of physician awareness.

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, physician's/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The physician is to notify the appropriate IRB/IEC or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

Adverse reactions that are suspected to be related to medicinal products other than evolocumab, should be notified by the physician to the competent authority in the Member State where the reactions occurred or to the marketing authorization holder of the suspected medicinal product in accordance with local reporting requirements.

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 physician must be obtained where applicable per local governing law and/or regulations. The IRB must be informed of all amendments and give approval. The physician **must** send a copy of the approval letter from the IRB to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the physician reserve the right to terminate the physician's participation in the study according to the contractual agreement. The physician is to notify the IRB 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

13.1 Publication Policy

The results of this study will be submitted for publication in the form of conference abstract(s) and journal manuscript(s).

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) 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, 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 contractual

agreement between the institution(s), physician(s), and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

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15. Appendices

Appendix A. List of Stand-alone Documents

The following stand-alone documents will be provided:

- Physician general questionnaire
- Subject telephone questionnaire

Appendix B. ENCePP Checklist for Study Protocols

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
Getting to an imprOved Understanding of LDL-C and Dyslipidemia management (GOULD): a Registry of High Cardiovascular Risk Patients in the United States

Study reference number:
20150230

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	9.1
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS register	☐	☒	☐	
1.1.6 Final report of study results.	☒	☐	☐	9.7.1.2

[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.

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
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)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8.1-8.3
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:
This is an observational study with no formal hypothesis

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☐	☐	☒	
3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☐	☐	☒	
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1
4.2.2 Age and sex?	☒	☐	☐	9.2.3.1
4.2.3 Country of origin?	☒	☐	☐	4, 9.1
4.2.4 Disease/indication?	☒	☐	☐	9.1.3
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g.	☒	☐	☐	9.1

ENCePP Checklist for Study Protocols (Revision 3)

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
event or inclusion/exclusion criteria)				

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☐	☐	☒	
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☐	☐	☒	
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.4
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☒	☐	☐	9.3.2

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☐	☐	☒	
7.1.1. Does the protocol address confounding by indication if applicable?	☐	☐	☒	
7.2 Does the protocol address:				
7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.9.1.3

ENCePP Checklist for Study Protocols (Revision 3)

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.9.1.2
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.3.3

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4
9.2 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 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.6.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.7

ENCePP Checklist for Study Protocols (Revision 3)

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.2 Are descriptive analyses included?	☒	☐	☐	9.7.2.1
10.3 Are stratified analyses included?	☒	☐	☐	9.7.2.3.2
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.7.2.3.3
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.9.4
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	4.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6, 9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.6

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9.1.3
12.1.2 Information bias?	☒	☐	☐	9.9.1.2
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.9.1.4
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.9.2

Comments:

Section 13: Ethical issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.2
13.3 Have data protection requirements been described?	☒	☐	☐	10.2, 10.3

ENCePP Checklist for Study Protocols (Revision 3)

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	12.1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	13
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	13.1

Comments:

Name of the main author of the protocol:

Date: 07/15/2016

Signature: _____

ENCePP Checklist for Study Protocols (Revision 3)

Appendix C. Sample Safety Reporting Form(s)

AMGEN Study # 20150230 Repatha® (evolocumab)	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

US Fax Number: +888-814-8653

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? Repatha® evolocumab No / Yes	Prefilled Syringe No / Yes	Prefilled Autoinjector No / Yes	Automated Mini-Doser No / Yes	Outcome of Event -Resolved -Not resolved -Fatal -Unknown	Check only if event is related to study procedure eg, biopsy
				☐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 # 20150230 Repatha® (evolocumab)	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 #
Repatha® (evolocumab)	☒ open label							Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown
Prefilled Syringe	☒ open label							Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown
Prefilled Autoinjector/Pen *(SureClick® Autoinjector)*	☒ open label							Lot # ☐ Unknown Serial # ☐ Unavailable / Unknown
Automated Mini-Doser (AMD)	☒ 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)*

AMGEN Study # 20150230 Repatha® (evolocumab)	Electronic Adverse Event Contingency Report Form For Restricted Use

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

Date (Day Month Year)	Test											
	Unit											

Site Number	Subject ID Number

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

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

Appendix D. 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 E. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8853

1. Case Administrative Information

Protocol/Study Number: 20150230

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

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AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20150230

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.

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Appendix F. List of Amgen® Products in the United States

Brand / Generic name

Aranesp® (darbepoetin alfa)

Blincyto® (blinatumomab)

Corlanor® (ivabradine)

Enbrel® (etanercept)

Epogen® (epoetin alfa) (*recombinant*)

Imlygic™ (talimogene laherparepvec)

Kyprolis® (carfilzomib)

Neulasta® (pegfilgrastim)

Neupogen® (filgrastim)

Nexavar® (sorafenib) tablets

Nplate® (romiplostim)

Prolia® (denosumab)

Repatha® (evolocumab)

Sensipar® (cinacalcet) tablets

Vectibix® (panitumumab) (*injection for IV infusion)*

Xgeva® (denosumab)