**Protocol Summary**

| | |
|---|---|
| Title of study | A post-marketing surveillance study for Repatha Inj. (evolocumab) in Korea (Protocol No.: 20160156) |
| Protocol version | 1.1 |
| Date of final protocol version | [redacted] |
| Study (PAS) Enrollment No. following EU approval | NA |
| Active ingredient | Evolocumab, AMG 145 |
| Brand name | Repatha Inj. |
| Reference drug | NA |
| Procedure No. | NA |
| Sponsor | Amgen Korea |
| Associated PASS | None |
| Objective of study | To assess the safety and efficacy of Repatha Inj. in post-marketing routine clinical settings |
| Country of study | Korea |
| Author | [redacted] |

[redacted]

## Investigator's agreement

I have read the attached post-marketing surveillance study protocol for Repatha Inj. (evolocumab) in Korea, dated [redacted], and agree to comply with all provisions specified herein.

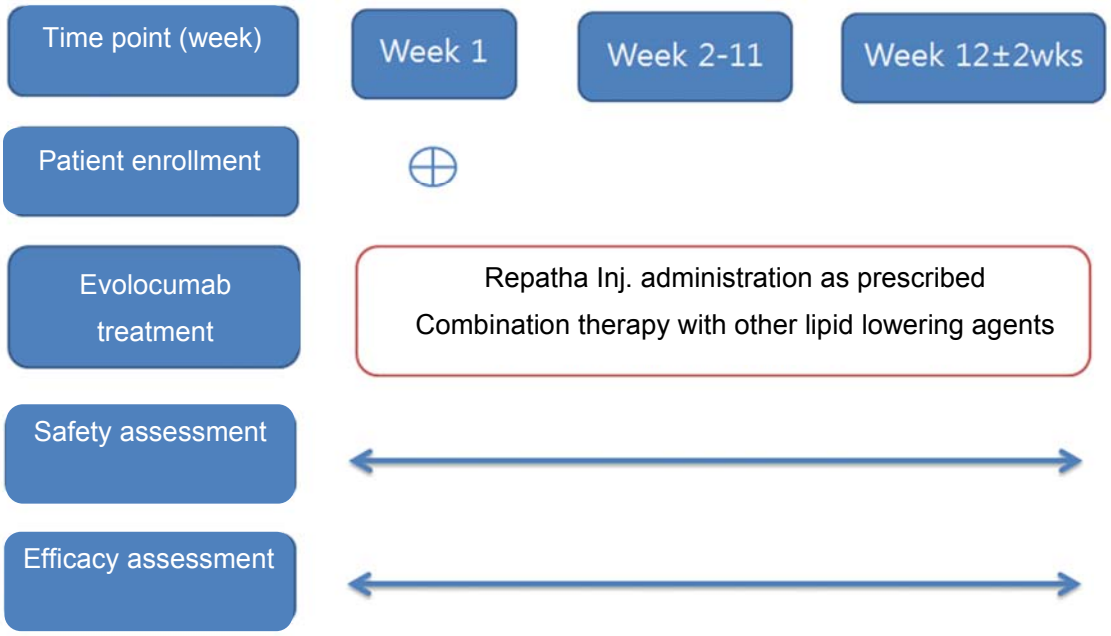
I agree not to use the confidential information contained in this document for any purposes other than the assessment and conduct of the study without the prior written consent of Amgen.

Signature

Name of investigator

Date (YYYY/MMM/DD)

## Diagram of study design



## 1. Table of contents

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## 2. List of abbreviations

| | |
|---|---|
| ADE | Adverse device effect |
| ADR | Adverse drug reaction |
| AE | Adverse event |
| CABG | Coronary artery bypass graft |
| CKD | Chronic kidney disease |
| CRF | Case report form |
| CVD | Cardio vascular disease |
| eGFR | estimated Glomerular filtration rate |
| FH | Familial hypercholesterolemia |
| FSE | First subject enrolled |
| HoFH | Homozygous familial hypercholesterolemia |
| ICJME | International committee of medical journal editors |
| IRB | Institutional review board |
| LDL-C | Low-density lipoprotein cholesterol |
| LDL-R | Low-density lipoprotein receptor |
| LSLV | Last subject last visit |
| MedDRA | Medical dictionary for regulatory activities |
| MFDS | Ministry of food and drug safety |
| PAD | Peripheral arterial disease |
| PCI | Percutaneous coronary intervention |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| PT | Preferred term |
| RMP | Risk management plan |
| SAE | Serious adverse event |
| SADR | Serious adverse drug reaction |
| SD | Standard deviation |
| SOC | System organ class |
| SOP | Standard operating procedure |
| TC | Total cholesterol |
| TG | Triglyceride |
| WHO ATC code | World health organization anatomical therapeutic chemical code |

## 3. Person in charge

| | |
|---|---|
| Sponsor: | Amgen Korea |
| Study physician: | Investigator at the study institution with study contract, Korea |

## 4. Synopsis

- **Title of study**

A post-marketing surveillance study for Repatha Inj. (evolocumab)

- **Study background and rationale**

According to Rule on Safety of Drugs etc. in Korea (enforced 01 Jul 2015), an applicant for product approval is responsible for submitting risk management plan for new drugs, orphan drugs, drugs acknowledged by the Minister of Food and Drug Safety for required submission of risk management plan, or drugs for re-examination for marketing authorization application.
In addition, according to Article 32 of Pharmaceutical Affairs Act, Article 22 of Rule on Safety of Drugs etc., and Regulation on Re-examination of New Drugs etc. (Ministry of Food and Drug Safety [MFDS] Notification No. 2016-97), it is required to conduct a study on the safety and efficacy of the drug for 6 years from the date of drug approval in the target number of patients calculated based on the prevalence of the applicable indication.
Amgen has submitted an application for marketing authorization of Repatha Inj. as combination therapy with other cholesterol lowering agents in adults and adolescents aged 12 or older with Homozygous Familial Hypercholesterolemia (HoFH).

- **Study questions and objectives**

1) Primary objective

The primary objective of this study is to assess the incidence rate of adverse events (AEs) (including device related AEs) and adverse drug reactions (ADRs) for up to 12 weeks in patients who are prescribed Repatha Inj. according to the approved therapeutic indications, dosage, and administration in post-marketing settings (see Section 11 for definitions of terms). In addition, profiles of AEs and ADRs will be analysed.

2) Secondary objective

The secondary objective of this study is to assess the efficacy of Repatha Inj. and to identify the characteristics of treated patients (e.g., demographics and medical history).

- **Study design/type**

This is a single arm, prospective, observational study. To meet the criteria and form recommended by the MFDS, the safety and efficacy of Repatha Inj. will be assessed in post-marketing settings for 6 years after drug approval in the target number of patients calculated based on the prevalence of the indication.

- **Subjects/data collection**

1) Subjects

Patients who meet the inclusion/exclusion criteria for this study will be enrolled for 6 years after approval of Repatha Inj. in Korea.

2) Data collection

The study drug, Repatha Inj., is available in the market for prescription by the investigator for therapeutic purposes.

Case report forms (CRFs) will be designed to collect the primary endpoint, secondary endpoints, and other study item related information from baseline and throughout the follow-up period. The investigator (the treating physician participating in this study) should prepare the CRFs.

- **Summary of subject eligibility criteria**

1) Inclusion criteria

- HoFH patient treated with Repatha Inj. according to the approved therapeutic indications, dosage, and administration in post-marketing settings
- Patient who voluntarily provided written informed consent

2) Exclusion criteria

- Patient who did not provide written informed consent
- There are no other exclusion criteria.

- **Follow-up**

Each patient will be followed up from the first Repatha Inj. dose to Week 12 of treatment, death, or lost to follow-up (e.g., patient transfer to another hospital), whichever is earlier.

- **Endpoints**

1) Primary endpoint

The primary endpoint is the incidence rate of AEs/ADRs observed or reported to the investigator during the follow-up period. All AEs will be classified using Medical Dictionary for Regulatory Activities (MedDRA).

If sufficient data is collected, seriousness and causal relationship to drug or device can be also analyzed.

2) Secondary endpoints

- Efficacy measurement; change in low-density lipoprotein (LDL)-cholesterol (LDL-C) measured as part of routine clinical practice from baseline to the end of follow-up
- Patient characteristics (for details, see Section **Error! Reference source not found.**.)
  - Demographic information and medical history
  - Diagnosis of hypercholesterolemia
  - Concomitant medication prior to study participation
  - Other concomitant medication

- **Number of subjects**

Amgen plans to follow up 10 patients who meet the inclusion/exclusion criteria for this study for 6 years after approval of Repatha Inj. in Korea.

Based on the low diagnosis rate and prevalence of HeFH (1/160,000 ~ 1,000,000 individuals), number of subjects estimated is approximately 10 subjects. [1]

- **Data analysis**

Categorical variables will be summarized with frequency and percentage, and continuous variables will be summarized with mean, standard deviation (SD), standard error (SE), median, Q1, Q3,

minimum, and maximum. Subject disposition, demographic information, and baseline characteristics will be summarized in the safety set.

For safety analysis, number of subjects, number of events, and incidence rate will be presented in the safety set for AEs (including device related AEs), ADRs, and serious AEs (SAEs). 95% confidence interval will not be calculated because it is not meaningful for the planned sample size of 10 subjects. For efficacy analysis, change (%) in LDL-C at Week 12 from baseline will be analysed in the efficacy set.

## 5. Amendments and updates

Not applicable

## 6. Milestone

- Expected date of protocol approval: [redacted] (approval of the draft by Amgen); The final approval is expected to occur when drug approval is obtained from the MFDS.
- Expected date of study initiation (first subject enrolled): [redacted] (The actual date of market release is subject to change according to the market release schedules in Korea.)
- Planned study institutions: all institutions that agree to participate in the study and treat HoFH patients with Repatha Inj. (approximately 30 institutions)
- Expected subjects/patients: All HoFH patients who agree to participate in this study and are prescribed Repatha Inj. (10 patients)
- Planned duration of enrollment/data collection: Patients will be enrolled for 6 years after approval of Repatha Inj.; Data will be collected until the last subject completes his/her last visit.
- Duration of study (e.g., duration from the first subject enrolment to the last subject's last visit); 6 years and 3 months
- Duration of observation for individual subjects: 12 weeks
- Expected date of final report: within 3 months after the end of re-examination period

## 7. Study rationale and background

### 7.1. Disease and therapeutic indication

HoFH is a genetic disorder primarily caused by homozygous mutations of the LDL receptor (LDLR) gene. HoFH is most commonly caused by mutations of both alleles of LDLR, resulting in decreased uptake and removal of LDL. HoFH patients with LDLR gene mutations may be either true homozygotes (having the same mutation in both alleles of LDLR) or compound heterozygotes (having different mutations in each allele of LDLR). Patients with HoFH may have severe hypercholesterolemia associated with LDL-C accumulation in plasma, tendon, and skin, and develop progressive atherosclerosis and, particularly coronary heart disease, typically within 20 years from birth. Worldwide, the prevalence of HoFH is estimated to be 1/160,000 to 1,000,000 individuals.[1]

### 7.2. Study rationale

According to Rule on Safety of Drugs etc. in Korea (enforced 01 Jul 2015), an applicant for product approval is responsible for submitting risk management plan for new drugs, orphan drugs, drugs acknowledged by the Minister of Food and Drug Safety for required submission of risk management plan, or drugs for re-examination for marketing authorization application.
In addition, according to Article 32 of Pharmaceutical Affairs Act, Article 22 of Rule on Safety of Drugs etc., and Regulation on Re-examination of New Drugs etc. (MFDS Notification No. 2016-97), it is required to conduct a study on the safety and efficacy of the drug for 6 years from the date of drug approval in the target number of patients calculated based on the prevalence of the applicable indication.

### 7.3. Statistical inference (assumption or hypothesis)

There is no formal hypothesis to be tested in this study. Instead, the proposed post-marketing surveillance study will provide descriptive data for the safety and efficacy of Repatha Inj. in routine clinical settings after marketing approval with HoFH patients in Korea.

### 7.4. Product background

Repatha Inj. (evolocumab) is a fully human monoclonal IgG2 antibody designed to inhibit Proprotein Convertase Subtilisin/Kexin type 9 (PCSK9).
Upon parenteral administration, Repatha Inj. (evolocumab) inhibits the binding of circulating PCSK9 to LDLR on liver cells, thereby interfering with PCSK9-mediated LDLR degradation. This increases LDLR levels in liver, resulting in a decrease in associated blood LDL-C levels.

## 8. Study questions and objectives

### 8.1. Primary objective

The primary objective of this study is to assess the incidence rate of AEs (including device related AEs) and ADRs for up to 12 weeks in patients who are prescribed Repatha Inj. in post-marketing settings (see Section 11 for definitions of terms). In addition, profiles of AEs and ADRs will be analysed.

### 8.2. Secondary objective

The secondary objective of this study is to assess the efficacy of Repatha Inj. and to identify the characteristics of treated patients (e.g., demographics and medical history).

### 8.3. Exploratory objective

Not applicable

## 9. Study methodology

This is a single arm, prospective, observational study. To meet the criteria and form recommended by the MFDS, the safety and efficacy of Repatha Inj. will be assessed in post-marketing settings after drug approval in patients treated with this drug according to the approved therapeutic indications, dosage, and administration.

### 9.1. Study design

This is a single arm, prospective, multicentre, observational study in HoFH patients treated with Repatha Inj. in Korea. According to regulatory guidelines, duration of enrolment is 6 years after drug approval in Korea.
Each patient will be followed up from the first Repatha Inj. dose to Week 12 of treatment, death, or lost to follow-up (e.g., patient transfer to another hospital), whichever is earlier.

### 9.2. Setting and subjects

#### 9.2.1. Duration of study

Planned duration of enrollment/data collection: Patients will be enrolled for 6 years after approval of Repatha Inj., and data will be collected until 12 weeks of last subject's enrollment.

#### 9.2.2. Selection and number of study institutions

Amgen will prepare a list of potential institutions/investigators who can prescribe Repatha Inj. in post-marketing settings. Based on this data, Amgen will visit each of the potential institutions prior to study initiation to evaluate feasibility of the institutions and to confirm the potential investigators' interest in and willingness for study participation. Study institutions will be selected based on the results of these pre-study site visits. Before the study begins, initiation visits will be carried out to

complete site trainings for the protocol and other study specific procedures. At the initiation visits, it will be emphasized that all eligible patients should be enrolled according to the protocol.

### 9.2.3. Subject eligibility

#### 9.2.3.1. Inclusion criteria

- HoFH patient treated with Repatha Inj. according to the approved therapeutic indications, dosage, and administration in post-marketing settings
- Patient who voluntarily provided written informed consent

#### 9.2.3.2. Exclusion criteria

- Patient who did not provide written informed consent
- There are no other exclusion criteria.

### 9.2.4. Matching

Not applicable

### 9.2.5. Baseline period

Before the first dose of Repatha Inj. is administered, baseline data (e.g., clinical laboratory tests, concomitant medication) will be collected (the latest time point prior to the first Repatha Inj. dose).

### 9.2.6. Follow-up

Each patient will be followed up from the first Repatha Inj. dose to Week 12 of treatment (window period for data collection: 10-14 weeks), death, or lost to follow-up (e.g., patient transfer to another hospital), whichever is earlier.

## 9.3. Endpoints

1) Primary endpoint

The primary endpoint is the incidence rate of AEs(including device related AEs)/ADRs observed or reported to the investigator during the follow-up period. All AEs will be classified using MedDRA. If sufficient data is collected, seriousness and causal relationship to drug or device can be also analyzed.

2) Secondary endpoints

- Efficacy measurement; change in LDL-C measured as part of routine clinical practice from baseline to the end of follow-up
- Patient characteristics (for details, see Section **Error! Reference source not found.**.)
  - Demographic information and medical history
  - Diagnosis of hypercholesterolemia
  - Concomitant medication prior to study participation
  - Other concomitant medication

### 9.3.1. Observation and data collection

See Figure 1 below for study diagram.

Figure 1 Overview of variables to be collected during the study

| Procedure | Week 1 | Weeks 2-11 | Week 12±2 weeks |
|---|---|---|---|
| Patient enrollment for evolocumab treatment | Administer Repatha Inj. according to prescription | | |
| | X | | |
| CRF (bseline) | X | | |
| CRF (Repatha Inj. dose and number of doses administered)[a] - Cumulative data through follow-up | ← | → | |
| CRF (LDL-C)[b] - Cumulative data through follow-up | ← | → | |
| CRF (safety) | → | | |

a. All information verifiable through follow-up will be collected.
b. There is no established procedure to collect LDL-C data in this study. Only the information verifiable through follow-up will be collected.

A patient who provides written informed consent and meets the inclusion/exclusion criteria will be considered eligible for enrollment in this study. Once the patient is enrolled, baseline data including demographic information should be collected in the CRF. Repatha Inj. treatment and LDL-C measurement information will continue to be collected during the follow-up period. AEs and other safety information will be also collected during the follow-up period.

<u>At baseline, the following patient characteristics and variables will be collected in the CRF.</u>

- Diagnosis of HoFH: duration of disease, family history, physical examination findings (tendinous xanthoma, cutaneous tuberous xanthoma), genetic test
- Demographic information: gender, date of birth, height, body weight, waist line, inpatient/outpatient
- Medical history: coronary artery disease (surgery; coronary artery bypass graft [CABG], percutaneous coronary intervention [PCI]), allergy, concomitant underlying disease (myocardial infarction, angina pectoris, heart failure, cerebral infarction [including psychogenic embolism], cerebral hemorrhage, peripheral arterial disease [PAD], hypertension [systolic and diastolic blood pressure measurements], diabetes mellitus [including impaired glucose tolerance, HbA1c], cognitive deficits [cerebrovascular/Alzheimer's disease type]), liver function (Child-Pugh class; A, B, or C), kidney function (chronic kidney disease [CKD], eGFR), and other medical conditions that may affect the safety and efficacy of evolocumab treatment.
- Concomitant medication:
  - ✓ Prior (8 weeks before baseline) and concomitant medication: statins (drug name, dose, duration of treatment), other medications for hypercholesterolemia
  - ✓ Concomitant treatment for hypercholesterolemia: medical diet, medical exercise, LDL-apheresis (8 weeks before baseline, date), apheresis, and other treatment
  - ✓ Other therapeutic drugs for concomitant disease: low-dose aspirin, warfarin, non-Vitamin K antagonists, oral anticoagulants, estrogen, steroids, or non-steroidal anti-inflammatory drugs for hypertension, diabetes mellitus, heart attack, angina pectoris, and arrhythmic disorder
- Lifestyle: smoking (past, current), alcohol consumption, exercise.

For safety assessment, all AEs and other safety information (e.g., pregnancy and lactation), if possible, will be collected through follow-up.

For efficacy assessment, LDL-C levels measured as routine clinical practice will be collected from baseline (the latest time point prior to the first Repatha Inj. dose) to the end of follow-up. Although LDL-C measurement cannot be required as part of the study procedures, LDL-C level monitoring is recommended as standard of care. Drugs administered over the period of 8 weeks prior to baseline will be collected as concomitant medication.

#### 9.3.2. Assessment of exposure
Not applicable

#### 9.3.3. Assessment of results
AEs (including SAEs and ADRs) and other safety information will be collected throughout the follow-up period, if possible, in the CRF and applicable safety reporting forms. Clinical laboratory test values and LDL-C levels measured during visits will be collected in the CRF at baseline (Week 0), at Week 12 (range: 10-14 weeks), or at the end of follow-up if the subject did not complete the 12 week treatment.

#### 9.3.4. Assessment of covariates
Not applicable

#### 9.3.5. Validity and reliability
Not applicable

### 9.4. Data source
The source of data to be used in this study is the patient's medical records. In addition, data will be also collected through the CRFs completed by the investigator. Laboratory test values will be measured at each institution according to the institutional standard practice.

### 9.5. Number of subjects
Amgen plans to recruit in a consecutive manner 10 patients who meet the inclusion/exclusion criteria for this study for 6 years after approval of Repatha Inj. in Korea.
Based on the low diagnosis rate and prevalence of HeFH (1/160,000 ~ 1,000,000 individuals), number of subjects estimated is approximately 10 subjects.[1]

### 9.6. Data management
Data will be managed according to applicable criteria and data cleaning procedures. Once the procedure for data quality management is completed, database will be locked. The original CRFs will be retained by Amgen Korea.

#### 9.6.1. Obtaining data files
Not applicable

#### 9.6.2. Linking data files
Not applicable

#### 9.6.3. Data quality checking and confirmation

A validated data system will be used for data collection. Data will be managed according to applicable standard operating procedure (SOP) under the supervision of Amgen Korea.
Once retrieved, the CRF will be checked for data integrity. Any missing data should be completed or accounted for by the investigator. The data obtained from the CRF will be transferred to the study database and verified. Exposure, results, and all other variables observed and measured at the institution will be collected through the data system. Data validation program will be used for standardized error checking. For logical discrepancies or obvious errors identified, a query will be sent to the investigator for confirmation and correction.
The investigator and study staff should verify the data against medical records, and the investigator will confirm and guarantee, by signing, the accuracy and integrity of the data corresponding to the information contained in the medical records. In addition, overlapping patients will be checked.
Details of quality assurance will be described in the data management plan.

### 9.7. Data analysis

#### 9.7.1. Planned analysis

##### 9.7.1.1. Interim analysis

According to local regulations, interim analyses will be performed for periodic reporting. Periodic reports should be submitted to the MFDS every 6 months for the first 2 years and every year thereafter until the end of re-examination period.

##### 9.7.1.2. Primary analysis

Not applicable

##### 9.7.1.3. Final analysis

Final analysis is planned to be performed once all study data are collected and cleaned (after database locking).

#### 9.7.2. Planned analysis methods

##### 9.7.2.1. Analysis sets

Data collected will be analyzed in the following analysis sets. For those subjects who are prematurely withdrawn, reasons for withdrawal will be described.
-Safety set: subjects who had at least one dose of the study drug and were followed up for safety at least once.
-Efficacy set: subjects in the safety set who were assessed for efficacy at least once.

##### 9.7.2.2. General considerations

All analyses will be performed with SAS 9.4 or higher version. In principle, two-sided statistical tests will be performed at a significance level of 5%, and up to two digits after the decimal point will be presented in summary statistics.

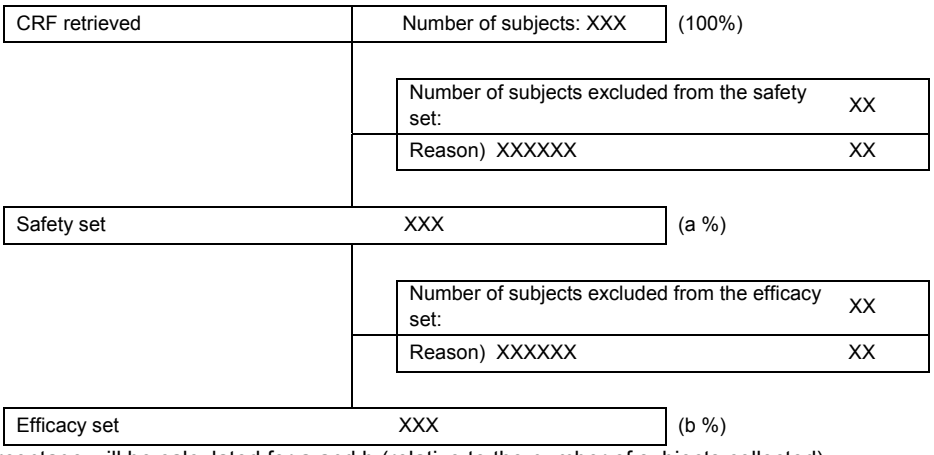
##### 9.7.2.3. Missing or incomplete data and lost to follow-up

In the event of missing data, observations will be used as they are for analysis, without corrections.

##### 9.7.2.4. Analysis of primary, secondary, and exploratory endpoints

###### 9.7.2.4.1. Disposition of subjects

All subjects collected will be summarized as below:




Percentage will be calculated for a and b (relative to the number of subjects collected).

#### 9.7.2.4.2. Subject characteristics

For demographic information of study subjects, categorical variables will be summarized with frequency and percentage, and continuous variables will be summarized with mean, SD, SE, median, Q1, Q3, minimum, and maximum. Subject information will be collected to identify patterns of drug use and will not be used as covariates for statistical analysis.

- Demographic information: gender (male, female), age (year), adult (≤65 years old, >65 years old), children (≤18 years old), pregnancy and lactation (yes, no), concomitant disease (yes, no), past medical history (yes, no), height, body weight, prior medication (yes, no)
- Lifestyle: status of smoking (ex-smoker, current smoker, non-smoker), alcohol consumption (current drinker, non-drinker), status of exercise
- All medical history collected will be standardized according to system organ class (SOC) and preferred term (PT). Based on the standardized SOC and PT, number of subjects (%) and number of events will be presented for past medical history.
- Past medical history: coronary artery disease (surgery; CABG, PCI), allergy, concomitant disease (myocardial infarction, angina pectoris, heart failure, cerebral infarction [including psychogenic embolism], cerebral hemorrhage, PAD, hypertension [systolic and diastolic blood pressure measurements], diabetes mellitus [including impaired glucose tolerance, HbA1c], cognitive deficits [cerebrovascular/Alzheimer's disease type]), liver function (Child-Pugh class; A, B, or C), kidney function (CKD, eGFR), and other medical conditions that may affect the safety and efficacy of evolocumab treatment.
- Other concomitant medication: all drugs, other than evolocumab, administered during the study period including enrolment visit; brand name, start date, end date, dose per administration, frequency of administration, route of administration, purpose of administration (indication), etc.
- Diagnosis of hypercholesterolemia: duration of disease (date of diagnosis), family history, physical examination findings (tendinous xanthoma, cutaneous tuberous xanthoma), genetic test (HeFH or HoFH)
- All drugs collected will be classified into prior or concomitant medication and will be standardized according to anatomical main group (Level 1) and therapeutic subgroup (Level 2) using World Health Organization Anatomical Therapeutic Chemical Code (WHO ATC code).

Based on the standardized Level 1 and Level 2, number of subjects (%) and number of events will be presented for prior and concomitant medication.

#### 9.7.2.4.3. Analysis of primary endpoint (safety)

AEs occurring during the study (including drug/device AEs and SAEs) will be summarized with number of subjects, number of events, and incidence rate.

#### 9.7.2.4.4. Analysis of secondary endpoints (efficacy)

- Percent (%) change in LDL-C at Week 12 from baseline
- Absolute change in LDL-C at Week 12 from baseline

### 9.7.2.5. Sensitivity analysis

Sensitivity analysis is not planned for this study.

#### 9.7.2.5.1. Subgroup analysis

Not applicable

#### 9.7.2.5.2. Stratified analysis

Not applicable

#### 9.7.2.5.3. Sensitivity analysis for residual confounding factors and bias

Not applicable

#### 9.7.2.5.4. Other sensitivity analysis

Other sensitivity analysis is not planned for this study.

### 9.7.3. Analysis of safety endpoints

See Section **Error! Reference source not found.**.

## 9.8. Quality control

Quality control will be performed by confirming that data management is operated according to data management SOP, all quality control results, including violations and measurements, are documented/reported, and violations, if applicable, are corrected as appropriate.

## 9.9. Limitation in study methodology

Because of its prospective, observational nature, this study is more greatly affected by bias than interventional clinical trials are. Below is the summary of methods to reduce common limitations and errors identified in this type of study.

- Missing and incomplete data including lost to follow-up

The investigator should be given clear guidelines for CRF completion for this study to ensure that he/she makes every effort to collect complete data.

- Selection bias, information bias, and confounding factors
  - Most patients treated with Repatha Inj. in post-marketing settings in Korea are expected to enroll in this study. This will be helpful in restricting selection bias.

- Amgen will prepare a list of potential institutions/investigators who can prescribe Repatha Inj. to HoFH patients in post-marketing settings. Based on this data, Amgen will visit each of the potential institutions prior to study initiation to evaluate feasibility of the institutions and to confirm the potential investigators' interest in and willingness for study participation. Study institutions will be selected based on the results of these pre-study site visits.
- Amgen will ask all known physicians who prescribe Repatha Inj. If a physician who was asked to conduct the study for Repatha Inj does not want to participate in the study, Amgen will record the reason in writing.
- Before the study begins, initiation visits will be carried out to complete site trainings for the protocol and other study specific procedures. At the initiation visits, the rareness of the disease will be explained, and the investigators will be asked to make every effort to enroll all eligible HoFH patients in a consecutive manner.
- There is a possibility that patients enrolled in this study (e.g., patients who will be treated with Repatha Inj.) are likely to have a severer form of the disease than those HoFH patients who are not prescribed Repatha Inj. (patients not included in the study). This confounding by indication bias would limit the generalization of safety and efficacy results.
- Analysis results should be interpreted with sufficient understanding of these study limitations. Of those, the most significant limitation is due to the very small number of patients to be enrolled. The very limited number of patients would limit the power of inference of this study because of lack of accuracy in estimation.

## 10. Patient protection

### 10.1. Informed consent

This study requires informed consent in order to collect medical information from patients treated with Repatha Inj. under conditions of routine clinical practice. The investigator cannot have a patient participate in the study without obtaining informed consent from that patient. Prior to study participation, the patient's written informed consent should be obtained and documented. At the time of informed consent, the patient will sign and date the written informed consent form (ICF). The original signed ICF should be retained by the investigator, and a copy of the signed ICF will be provided for the subject.

### 10.2. Institutional Review Board

This study will be conducted in compliance with applicable local regulations as well as Institutional Review Board (IRB) regulations. If necessary by regulation, an approval will be obtained prior to study initiation from an adequately established IRB. In addition, if necessary by regulation, the investigator is responsible for notifying the IRB of the safety information/cases subject to expedited reporting.

### 10.3. Confidentiality

The investigator should ensure that the patient confidentiality is maintained in the documents submitted to Amgen Korea.

The patient's medical information obtained as part of this study is confidential and should not be disclosed to a third party except for cases described below. The investigator/institution will allow Amgen and its representative, MFDS, and other regulatory authorities to have direct access to source document/data. This access can be provided during study related monitoring, audit/inspection, and IRB/MFDS review. Presentation of study results should be conducted

according to applicable local regulations, and personal information contained in the medical information should be kept confidential in these presentations.

## 11. Collection of safety information and product complaints

### 11.1. Definitions of safety events

#### 11.1.1. Adverse event

An AE is any unintended medical event occurring to a patient treated with a drug, regardless of causal relationship to the relevant treatment. Therefore, an AE can be any undesirable and unintended sign (e.g., laboratory test abnormalities), symptom, or disease occurring during treatment with the drug, and does not necessarily have to have a causal relationship to the relevant drug.

AEs are defined as:

- Exacerbation of a pre-existent condition or underlying disease, or
- An event related to drug withdrawal (e.g., development of a new symptom)

The investigator is responsible for assessing the causal relationship of an AE to Amgen Korea products before reporting the event to Amgen Korea.
Device (e.g., injection) related AEs are associated with device application and include insufficient or inappropriate instructions for application, malfunction, intentional misuse/overuse of device, or application error.

- ADRs

An ADR is any undesirable and unintended response occurring upon normal administration/use of a drug, in which causal relationship to the relevant drug cannot be ruled out. Spontaneously reported AEs with unknown causal relationship to the drug will be also regarded as ADRs.

- Unexpected ADRs

An unexpected ADR is an ADR that differ from the labeled information of the drug in the aspect of its nature, severity, specificity, or outcome.

#### 11.1.2. Serious adverse events

An SAE is any of the above defined AEs that:

- results in death,
- is life threatening,
- requires hospitalization or prolonged hospitalization,
- results in persistent or significant disability or incapacity,
- results in congenital anomaly or birth defect, or
- other medically important events that do not meet any of the above criteria.

Hospitalization that meets the above definition of ‘seriousness’ means overnight stay at a medical institute. ‘Other medically important events’ are important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events may include allergic bronchospasm, convulsions, blood dyscrasias, drug induced hepatic impairment, events requiring emergency room visits, outpatient surgery, or other events requiring emergency intervention.

#### 11.1.3. Other safety findings

Other safety information (irrespective of AE relationship) is as follows:

- Amgen drug product related medication error, accidental or intentional overdose, misuse, or overuse
- Exposure during pregnancy and lactation
- Transmission of infectious agents
- Reported use of the drug for purposes other than the approved indications, including off-label use
- Occupational exposure
- Lack or loss of the intended efficacy of the drug

#### 11.1.4. Product complaints

A product complaint is any written, electronic, or oral notification claiming defects of a product or device associated with its identity, quality, durability, reliability, safety, efficacy, or function after it is released by Amgen or its distributor or partner to be distributed to market or hospitals. These include drugs or devices provided and/or repackaged/modified by Amgen; drugs or devices include investigational products.

### 11.2. Requirements for safety reporting

The investigator is responsible for ensuring that the safety events (AEs, product complaints, and other safety information) identified by the investigator or reported by the patients during the data collection period described in **Figure 1** are recorded in the study documents and CRFs as appropriate.

SAEs and pregnancy/lactation events should be reported to Amgen within one business day after the investigator becomes aware of the event using Amgen safety reporting form (written or electronic).

See Appendix C for sample safety reporting form. See Appendix D for additional safety reporting information on criteria for the assessment of severity and causal relationship of AEs. See Appendix E for sample pregnancy and lactation reporting form.

The investigator may be asked to provide additional information for the reported event (e.g., hospital discharge summary or information excerpted from the medical records). The information provided for the relevant event should correspond to the information contained in the CRF where the safety data are recorded (e.g., Event CRF).

#### 11.2.1. Requirements for safety reporting to regulatory authorities

In compliance with pharmacovigilance guidelines and local regulations, Amgen will report safety data as required by the regulatory authorities, investigator/institution, IRB, or other applicable ethics committee. The investigator will inform the IRB or other applicable ethics committee of SAEs according to local procedures and regulations.

### 11.3. Protocol amendment and study termination

Amgen Korea may amend the study protocol at any time. If the protocol is amended, the investigator should comply with the protocol amendment.

## 12. Plans for dissemination and communication of study results

This study will be conducted for 6 years after approval of the product in Korea; data will be collected

until the last subject completes his/her last visit. The final study report is expected to be prepared by 3 months after database lock.

## 13. Publication policy

Study results will be submitted for abstract presentation at academic conferences or for publication in medical journals.
Authorship of the publications resulting from this study will be determined based on Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals by International Committee of Medical Journal Editors as specified below.

- Authorship should be based on (1) substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, (2) drafting the work or revising it for important 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 related to publication are appropriately investigated and resolved; the author should meet all of these four criteria.
- When a large multicenter organization has conducted the work, the organization should decide who will be directly responsible for the work. They should meet the criteria for authorship defined above.
- Acquisition of funding, data collection, or supervision of a research group alone cannot justify authorship.
- Anyone designated as an author is qualified for authorship, and everyone qualified should be included in the list.
- Each author must have participated in the work enough to be officially responsible for the appropriate portion of the work.

Prior to submission, all publications based on this study (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) should be reviewed by Amgen Korea and Amgen's corporate review procedures.

## 14. Compensation

Not applicable

## 15. Reference

1) Youngblom E, Knowles JW. Familial Hypercholesterolemia. 2014 Jan 2. In: Pagon RA, Adam MP, Ardinger HH, Wallace SE, Amemiya A, Bean LJH, Bird TD, Fong CT, Mefford HC, Smith RJH, Stephens K, editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2016. Available from http://www.ncbi.nlm.nih.gov/books/NBK174884/
PubMed PMID: 24404629.

## 16. Appendices

Appendix A List of monographs
Appendix B. ENCePP checklist for study protocol
Appendix C. Sample safety reporting form
Appendix D. Additional safety reporting information
Appendix E. Sample pregnancy and lactation reporting form

## Appendix A. List of monographs

None

## Appendix B. ENCePP checklist for study protocol

Not applicable at the time of submission for MFDS approval

## Appendix C. Sample safety reporting form

| Project ID: 20160156 | A | **Safety Reporting Form** Primary Data Collection | Date of Report: |
|---|---|---|---|
| | Fax reports to: Amgen Local Office 080-908-0982 | | |

1. Indicate event type: ☐ AE/Other safety finding ☐ AE/Other safety finding with Product Complaint ☐ Product Complaint only

| 2. Vendor Contact Details | | | 3. Reporter ID | | |
|---|---|---|---|---|---|
| name | phone | fax | Name or ID | phone | fax |
| address | | | address | | |
| city | state/province | | city | state/province | |
| postal code | country | | postal code | country | |

| 4. HCP Contact Details (if other than reporter) | | | 5. Patient | | | |
|---|---|---|---|---|---|---|
| name | | | Initials (optional) | Sex | Age (at time of event) | Was consent obtained to follow-up with HCP? ☐ Yes ☐ No |
| country | | | | ☐ F ☐ M | | |
| address | | | | | | |
| city | state/province | postal code | Weight ☐ lbs ☐ kg | Height ☐ in ☐ cm | Race | Is patient also reporter? ☐ Yes ☐ No |
| phone | fax | | | | | |

| 6. Medical History (include primary diagnosis) | 7. Suspect Product Information (include dosing details) | | | | |
|---|---|---|---|---|---|
| | Product: | | | | |
| | Indication: | | | | |
| | Start Date (day month year) | Stop Date (day month year) | Dose | Route | Freq |
| | | | | | |
| | | | | | |

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # ☐ Unknown

Serial # ☐ Unavailable / Unknown

Vial size

**8. AE, other safety finding, or product complaint information** — HCP ONLY

| Finding (List main event first; one event per line) | Onset Date (day month year) | Resolved Date (if patient died, list date of death) Cause of Death: _____ (provide autopsy report) (day month year) | Hospitalization Hospitalized? ☐ Yes ☐ No Hospitalization Prolonged? ☐ Yes ☐ No Admitting dx _____ (provide discharge summary) Date Admitted (day month year) Date Discharged (day month year) | Serious Criteria 01 Fatal 02 Immediately life-threatening 03 Required hospitalization 04 Prolonged hospitalization 05 Persistent or significant disability /incapacity 06 Congenital anomaly / birth defect 07 Other significant medical hazard | Action Taken 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=Drug rechallenge (state outcome) | Outcome 1=resolved 2=resolved w/ sequelae 3=resolving | Severity 1=mild 2=moderate 3=severe | Relationship to Product/ Device* Is there a reasonable possibility that this event may have been caused by the Product / Device? evolocumab | Device |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | |
| | | | | | | | | | |
| | | | | | | | | | |

**9. Description: chronological summary of symptoms or product complaint from above** (signs, diagnosis, treatment, concomitant medications including those used to treat event.)

* Relationship to product/device: 1) certainly, 2) Probable/likely, 3) Possible 4) unlikely 5) conditional/unclassified 6) unassessable/unclassifiable

Reporter Signature: _____ Page 1 of ____

The data provided by you will be transferred as a report to Global Safety at Amgen Inc (USA) and will be exclusively used for safety and quality purposes
For vendor surveys of Health Care Professionals

*FORM-067756 Ver. #: 3.0 Effective date: 07-Jul-2014* Page 1 of 1 *ADR Form Created: DD-MMM-YYYY*

## Appendix D. Additional safety reporting information

1) Assessment of severity of adverse events

Severity of AEs may be determined by the attending physician or by the patient's report. Severity should be assessed regardless of relationship to the drug, seriousness criteria, or cases.

| | |
|---|---|
| Mild | Signs and symptoms are tolerable and do not affect daily activities. |
| Moderate | Signs and symptoms are severe enough to interfere with daily activities and result in minimal restrictions. |
| Severe | Signs and symptoms are so severe that the patient is unable to carry out daily activities. |

2) Assessment of causal relationship to the study

① Certain

A clinical event occurring in a plausible time relationship to drug administration, and which cannot be explained by other drugs or chemicals or concurrent disease. The response to withdrawal of the drug should be clinically plausible. The event must be definitive pharmacologically or phenomenologically upon re-challenge of the drug as necessary.

② Probable/likely

A clinical event with a reasonable time sequence to administration of the drug, unlikely to be attributed to by other drugs or chemicals or concurrent disease, and which follows a clinically reasonable response upon withdrawal of the drug (re-challenge information is not available).

③ Possible

A clinical event with a reasonable time sequence to administration of the drug, but which could also be explained by other drugs or chemicals or concurrent disease. Information on drug withdrawal of the drug is lacking or unclear.

④ Unlikely

A clinical event with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals, or underlying disease provide plausible explanations.

⑤ Conditional/unclassified

A clinical event about which more data is essential for a proper assessment or the additional data is under examination.

⑥ Unassessable/unclassifiable

A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

## Appendix E. Sample pregnancy and lactation reporting form

### Pregnancy reporting form

**AMGEN™ Pregnancy Notification Worksheet**

***Fax Completed Form to the Country-respective Safety Fax Line***

**1. Case Administrative Information**

**Protocol/Study Number:** _____

**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

**Lactation reporting form**

AMGEN Lactation 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:** _____

**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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