

Summary Table of Study Protocol

Title	Long Term Post Marketing Specified Drug Use Result Survey for Evolocumab (AMG 145) in Japan (study number 20140409)
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Product Reference	
Procedure Number	
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Joint PASS	No
Research Question and Objectives	To assess safety and effectiveness of evolocumab in post-marketing real-world medical practice
Country(-ies) of Study	Japan
Author	 Manager, Post Marketing Surveillance, Global Patient Safety – Japan Amgen Astellas Biopharma K.K.

Marketing Authorisation Holder

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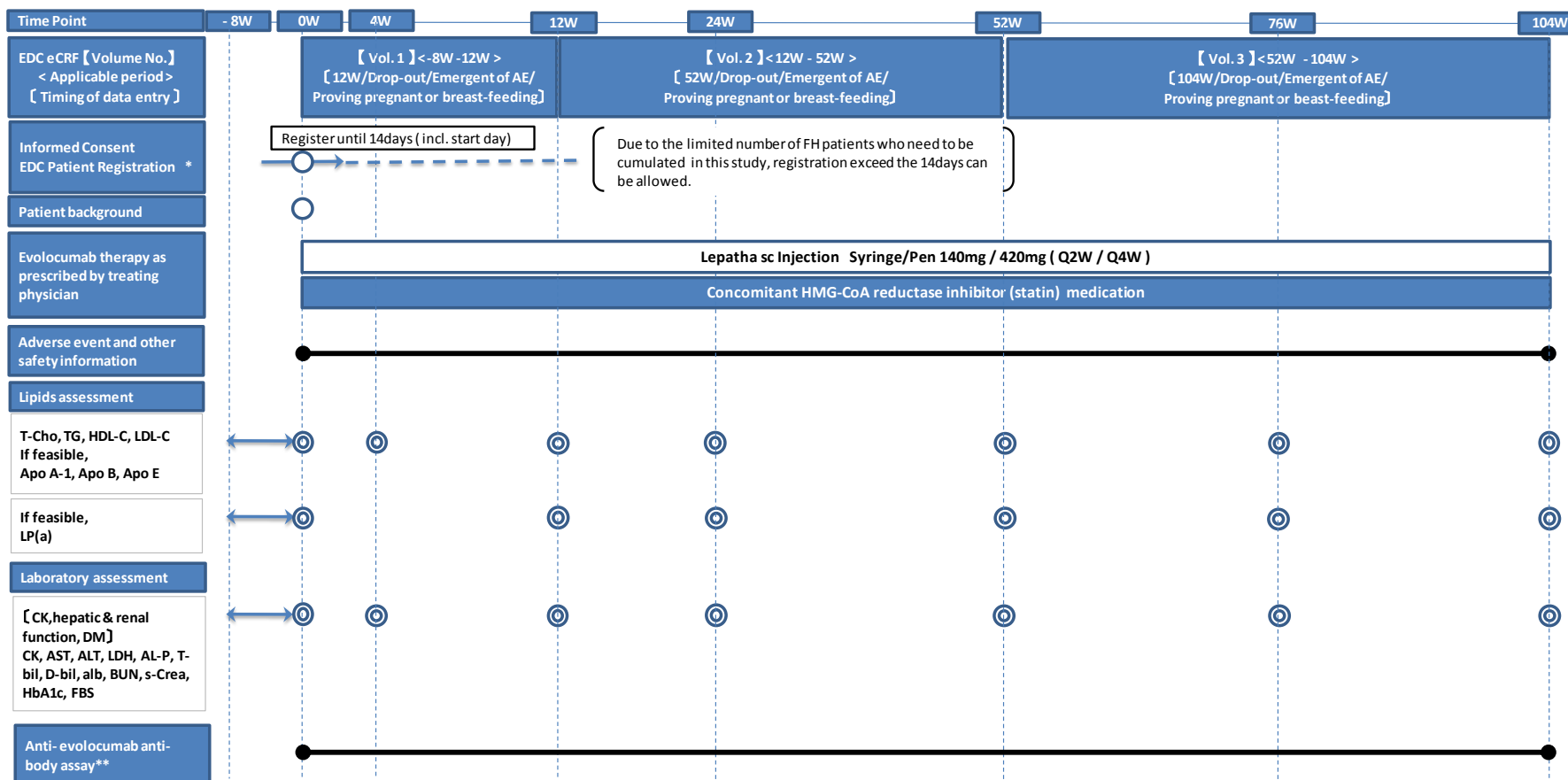
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Study Design Schema



*) After obtaining the written informed consent, patient registration is conducted within 14days after the start of evolocumab therapy (incl. start day). However, due to the limited number of Familial Hypercholesterolemia (FH) patients who need to be cumulated in this study, registration exceed the 14 days can be allowed. Especially, as to FH patients, all-case patient registration as much as possible, inclusive of inputting data and sending the case report form (EDC), at cooperative medical institutions is required. This study targets the FH patients who started the evolocumab therapy before concluding the contract with medical institutions, as well.

**) Anti-evolocumab anti-body assay is conducted by the procedure specified separately.

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2. List of Abbreviations

Abbreviations	Definition of the Terms
ADR	Adverse drug reaction
AE	Adverse event
Apo	Apolipoprotein
BMI	Body mass index
CI	Confidence interval
CKD	Chronical kidney disease
CRF (eCRF)	Case report form (electronic case report form)
CRO	Contract research organization
CVD	Cardio vascular disease
EC (IEC)	Ethical committee (Internally ethical committee)
EDC	Electronic data capture
EPPV	Early phase post-marketing vigilance
FH	Familial hypercholesterolemia
GPSP	Good Post-marketing Study Practice
HCPs	Health care professionals
HCV	Hepatitis C virus
HDL-C	High-density lipoprotein cholesterol
HMG-CoA	Hydroxymethylglutaryl coenzyme A
ICJME	International committee of medical journal editors
IgG2	Immunoglobulin G2
IRB	Institutional review board
JAS guideline	Japan atherosclerosis society guideline
J-NDA	Japan new drug application
J-PSUR	Japan periodic safety update report
J-RMP	Japan risk management plan
LDL-C	Low-density lipoprotein cholesterol
LDLR	Low-density lipoprotein receptor
Lp(a)	lipoprotein(a)
MR	Medical Representative
ORRG	Observational research review group (the function in the Amgen Inc.)
PAD	Peripheral arterial disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
PMDA	Pharmaceuticals and medical devices agency
PMS	Post marketing surveillance
Q	Quartile
Q2W	Every 2 weeks
Q4W	Every 4 weeks
SAP	Statistical analysis plan
SD	Standard deviation
total-C	Total cholesterol
ULN	Upper limit of normal

3. Responsible Parties

Sponsor: Amgen Astellas BioPharma K.K., Japan

Collaboration partner: Astellas Pharmaceutical Inc., Japan

Contract Research Organization (CRO):

[REDACTED]

Investigators: Investigators at medical institutions with active contracts for the survey, Japan

4. Abstract

- Study Title

Long Term Post Marketing Specified Drug Use Result Survey for Evolocumab (AMG 145) in Japan

- Study Background and Rationale

In the Japan new drug application (J-NDA) for evolocumab, safety and effectiveness data on about 700 Japanese subjects, including 145 subjects who will be followed for up to 12 months were presented. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

- Research Question and Objective

- Primary Objective

The primary objectives of study are to 1) determine the incidence of adverse events (AEs) and adverse drug reactions (ADRs: adverse events for which causal relation to evolocumab cannot be ruled out) among patients receiving evolocumab for up to 2 years (104 weeks), and 2) identify and describe patient characteristics (e.g. demographics, medical history) associated with the safety and effectiveness of evolocumab therapy for the patients with Familial Hypercholesterolemia (Heterozygous or Homozygous) and Hypercholesterolemia in the post-marketing real-world medical practice .

- Secondary Objective

None.

- Hypothesis(es)/Estimation

There is no hypothesis to be tested. Instead, the proposed survey will provide descriptive data on real-world use of evolocumab and adverse event occurrence in patients in Japan.

- Study Design/Type

Prospective observational study in post marketing setting without a comparator arm.

- Study Population or Data Resource

Patients for whom evolocumab is prescribed at participating medical institutions in accordance with the approved Japan prescribing information (i.e., those with Familial Hypercholesterolemia and Hypercholesterolemia who have high risk factors for cardiovascular event and do not respond sufficiently to Hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) for hypercholesterolemia.)

- Follow-up

2 years (104 weeks)

- Variables

- Outcome Variables

Safety: Adverse events (including seriousness and causal relation to drug or device) and other safety information (e.g. overdose, lack of effectiveness, pregnancy and lactation with or without adverse event)

Effectiveness: LDL-C, non-HDL-C, total-C, and triglyceride (values at baseline and after starting evolocumab injections, as measured as part of medical practice)

LDL-C: Low-density lipoprotein cholesterol

HDL-C: High-density lipoprotein cholesterol

Total-C: Total cholesterol

- Exposure Variables

Dosage and duration of evolocumab injection

- Study Sample Size

3000 patients with 2-year observation period, at least 6000 patients to be enrolled.

Sub-grouped of 300 patients with hepatic impairment and 300 elderly patients ≥ 75 years old patients with 2-year follow-up to be collected.

- Data Analysis

Patient disposition, demographics and baseline characteristics will be summarized.

Statistical test (chi-square, etc.) will be applied depending on the type of variable (nominal, ordinal, etc.).

5. Amendments and Updates

Amendment or update no	Date	Amendment or update and Reason
ver. 1.0	21 July 2015	Original version reviewed by Observational Research Review Group (ORRG) for Pharmaceuticals and Medical Devices Agency (PMDA) discussion
ver. 2.0	08 April 2016	Approved version by PMDA (Amendments based on the results of PMDA discussion. It is used for the start of data collection)

6. Milestones

[REDACTED]

[REDACTED]

[REDACTED] After the last patient enrolled to meet the expected sample size completes the observational period of 2 years (104 weeks), a data analysis will be performed and a final report summarizing the results of the survey will be completed by planned date as below.

For both interim and final analyses, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]

[illegible]

7.1 Diseases and Therapeutic Area

In Japan, 40.9% of patients with a history of hyperlipidemia and 42.3% of those with no history of hyperlipidemia had total cholesterol levels > 200 mg/dL (> 5.2 mmol/L) (Venkitachalam et al, 2012). Despite widespread use of statins and other lipid-lowering therapies, many patients do not reach their target LDL-C goals and there remains a substantial unmet medical need. A large cross-sectional study conducted in Japan found that among patients being treated with lipid-lowering therapies, 24.6% of primary prevention patients and 55.5% of secondary prevention patients did not achieve LDL- goals, as defined by 2007 Japan atherosclerosis society guideline (JAS guidelines, Takahashi, 2013).

Evolocumab is a fully human monoclonal immunoglobulin G2 (IgG2) directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab binds selectively and with high affinity to PCSK9 and inhibits circulating PCSK9 from binding to the low-density lipoprotein receptor (LDLR) on the liver cell surface, thus preventing

PCSK9 mediated LDLR degradation. Increasing liver LDLR levels results in associated reductions in serum LDL-C. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C.

7.2 Rationale

[REDACTED]

7.3 Statistical Inference (Estimation or Hypothesis [es])

There is no formal hypothesis to be tested. Instead, the proposed survey will provide descriptive data on real-world use of evolocumab and adverse event occurrence in patients in Japan. While the survey does not target any specific patient sub-populations, it will collect data on the patient characteristics with respect to “important missing information for safety” in J-RMP.

8. Research Question and Objectives

To obtain the safety information and effectiveness of the product in the real-world use of evolocumab in Japan.

8.1 Primary

The primary objectives of study are to 1) determine the incidence of AEs and ADRs among patients receiving evolocumab for up to 2 years, and 2) identify and describe patient characteristics (e.g. demographics, medical history) associated with the safety and effectiveness of evolocumab therapy for the patients with Familial Hypercholesterolemia (Heterozygous or Homozygous) and Hypercholesterolemia in the post-marketing real-world medical practice.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9. Research Methods

9.1 Study Design

A non-interventional (observational) survey of patients in Japan who will be treated with evolocumab in the post-marketing setting without comparator arm.

9.2 Setting and Study Population

The patients (up to the number of patients specified in an agreement with each medical institution) for whom evolocumab is prescribed at participating medical institutions will be registered within 14 days after the start of evolocumab treatment (incl. start day)* without further eligibility criteria, so that data can be collected on how evolocumab will be used in Japan, including patient sub-populations for which existing data are limited or non-existent (i.e., what is listed as “important missing information” in J-RMP).

*) After obtaining the written informed consent, patient registration is conducted within 14 days after the start of evolocumab treatment (incl. start day). However, due to the limited number of Familial Hypercholesterolemia (FH) patients who need to be cumulated in this study, registration exceed the 14 days can be allowed. Especially, as to FH patients, all-case patient registration as much as possible, inclusive of inputting data and sending the case report form (EDC), at cooperative medical institutions is required. This study targets the FH patients who started the evolocumab therapy before concluding the contract with medical institutions, as well.

9.2.1 Study Period

Enrollment (registration) Period : 6 June 2016 – 30 April 2020

Data Collection Period : 6 June 2016 – 30 April 2022

9.2.2 Selection and Number of Sites

To be eligible for the survey, medical institutions must accept the adoption and delivery of evolocumab and be able to participate in and implement the survey with EDC. Medical Representatives (MRs) will explain the objectives, target subjects, and method of survey to the physicians at eligible institution who would be in charge of the survey, and request the implementation of the survey to the head of the institution (e.g. director), and the agreement in writing is then executed with the institutions after

undergone the deliberation at IRB (Institutional Review Board) / EC (Ethical Committee) (or external EC, if not equipped internally).

About [REDACTED] medical institutions [REDACTED] and [REDACTED] medical experts of committing participation and co-operation of the study.

9.2.3 Patient/Healthcare Professional Eligibility

9.2.3.1 Inclusion Criteria

Patients for whom evolocumab is prescribed at participating medical institutions in accordance with the approved Japan prescribing information (i.e., those with Familial Hypercholesterolemia (Heterozygous or Homozygous) and Hypercholesterolemia who have high risk factors for cardiovascular event and do not respond sufficiently to HMG-CoA reductase inhibitor (statin) for hypercholesterolemia).

9.2.3.2 Exclusion Criteria

No exclusion criteria are applied. When off-label use is noted, data will be collected but the investigator (prescribed) will be reminded of the approved indication.

9.2.4 Matching

No matching is used.

9.2.5 Baseline Period

The period for the purpose of collecting baseline data (e.g., laboratory tests, concurrent medication) is defined as 8 weeks before the first SC injection (index date).

9.2.6 Study Follow-up

Each patient will be followed for up to 2 years (104 weeks).

The end of follow-up for each patient is defined as death, loss to follow-up (e.g., patients transferring to another clinic), 30 days from the last administration of evolocumab, or 2 years from the first evolocumab prescription, whichever occurs first. No stopping rules will be applied to this non-interventional survey.

9.3 Variables

Information described in Sections 9.3.1-9.3.3 is collected in 3 electronic case report forms (eCRFs: vol.1, vol.2 and vol.3) per a patient. Vol. 1 is used to collect data from baseline, week 4, and week 12; vol. 2 is used to collect data from week 24 and week 52; vol.3 is from week 76 and week 104. Adverse event and other safety information are collected throughout the follow-up period.

9.3.1 Exposure Assessment

Dosage, period (start/end date), frequency of injection (Every 2 weeks (Q2W), Every 4 weeks (Q4W)), drug withdrawal (Yes or No, date, reason) and injection site (upper arm, abdomen, thigh) of evolocumab are collected in eCRF (volumes 1, 2 and 3).

9.3.2 Outcome Assessment

Adverse events (including seriousness and causal relations to drug or device), inclusive of reaction at local injection sites, and other safety information (e.g. overdose, lack of effectiveness, pregnancy and lactation with or without adverse event) are collected as they become available throughout the follow-up period by using eCRF and applicable safety reporting form.

Lipids Laboratory values for LDL-C, HDL-C, total-C, and triglyceride, if feasible, Apolipoprotein (Apo) A1, Apo B, Apo E and lipoprotein(a) (Lp(a)) measured as a part of routine medical practice, are collected in eCRF for baseline (ranged:-8W-0W), 4W (2-6W) [excluding Lp(a)], 12W (8-16W), 24W (20-28W), 52W (48-56W), 76W (72W-80W) and 104W (100W-108W) or at the end of follow-up.

9.3.3 Covariate Assessment

Data on the following covariates are collected in patient registration form and eCRF.

Patient information for registration: patient ID, sex, birth year/month, date of informed consent, start date of evolocumab injection, reason for usage (diagnosis: Familial Hypercholesterolemia [Heterozygous or Homozygous] and Hypercholesterolemia)

Patient demographics and medical history: height, weight, Body Mass Index (BMI), waist circumference, inpatient/outpatient, menopause, medical history of allergy, alcohol consumption, reason for usage. genetic test (for Familial Hypercholesterolemia [Heterozygous or Homozygous]), tendon xanthoma, skin tuberous xanthoma, duration of illness, medical history of coronary artery disease, diabetes mellitus/ impaired glucose intolerance, chronic kidney disease (CKD), non-cardioembolic stroke, peripheral arterial disease (PAD), smoking (past, present), hypertension (systolic and diastolic blood pressure values), low HDL-C value (<40mg/dL), family history of premature coronary artery disease, other medical history (name of disease), Hepatitis C virus (HCV) infection (negative, positive, amount of virus), dementia, other preexisting disease (name of disease), hepatic and renal dysfunction (grade, [see Appendix F])

Pregnancy and lactation (during observation period)*: gestation period, stage of pregnancy, expected date of delivery

*: Avoid or discontinue evolocumab sc injection to breast feeding women, pregnant women and women anticipating pregnancy since evolocumab therapy should be concomitant with HMG-CoA reductase inhibitor (statin) medication.

Concomitant medication of statin and other treatment for hypercholesterolemia: medicine name, duration, dosage

Concomitant therapy of LDL-apheresis: duration, interval, timing of evolocumab therapy.

Non-medicine therapy: medical diet, therapeutic exercise.

Other concomitant medicine: medicine name, duration, dosage

9.3.4 Validity and Reliability

It is a prospective, observational cohort study, so variables, which can be measured at medical sites in the real-world medical practice, are selected for this survey in reference to prior evolocumab clinical trials and advice from local medical experts.

Exposures, outcomes, and all other variables observed and measured by each medical site will be collected through EDC system. Standardized error check program is installed in EDC system and generates alerts automatically. If a logical discrepancy in eCRF and clear error is identified, a query form will be prepared and delivered to the institutional site physicians for clarification and correction. Site physicians and staff are requested to check the data against medical records, and accuracy and completeness of data consistent with information in medical records is confirmed and attested by electronic signature of investigators.

9.4 Data Sources

The original source of the data used in the survey is patient medical records. Data are collected through eCRFs, which are populated by the investigators.

Laboratory test values among variable data will be measured by each medical site with their own method.

9.5 Study Size

The target of 3000 patients with 2-year (24-month) observation period for eligible safety analysis has been set for 95% statistical power to detect at least 1 patient experiencing an adverse event with a 2-years incidence of 0.1%. The sample size of

6000 enrolled patients over the 4-years enrollment period has been chosen to achieve the above target for 2-year follow-up data with an assumed discontinuation (loss to follow-up) rate of 50%. The discontinuation rate of 50% was estimated based on the discontinuation rate of 43% in the Japanese post marketing surveillance of 2 years for HMG-CoA reductase (statin) administration. Additional considerations were made regarding the difference in the mode of administration as well as the difficulty to follow patients who will be transferred from specialized care hospitals to general practice clinics. Consequently, it was estimated that enrollment of at least 6000 patients will be needed. In the Japanese real-world medical practice, based on the results of post marketing surveys for statins, 12.2% - 19.3% (weighted mean 17.3%) of patients were ≥ 75 years old, and 7.7 – 24.5 % (weighted mean 10.3%) of patients prescribed statins have hepatic impairment. Therefore, it is expected that 300 patients of 3000 patients with 2-year follow-up data would be ≥ 75 years old and patients with hepatic impairment, respectively, in the real-world medical practice in Japan. Both sample sizes of sub-grouped will enable a meaningful safety evaluation of patients with ≥ 75 years old and hepatic impairment.

9.6 Data Management

Data collection is conducted by using a validated EDC and eCRF system, developed by an external service provider, Fujitsu FIP, Tokyo, Japan.

Data management is conducted by another external service provider, Bell Medical Solution Inc. Tokyo, Japan under its own standard operating procedure with oversight by the Amgen Astellas BioPharma K.K.

9.6.1 Obtaining Data Files

Not applicable.

9.6.2 Linking Data Files

Not applicable.

9.6.3 Review and Verification of Data Quality

Quality and completeness will be annually confirmed by self-inspection per the local good post-marketing study practice (GPSP).

9.7 Data Analysis

Patient disposition, demographics and baseline characteristics will be summarized. Statistical test (chi-square, etc.) will be applied, depending on the type of variable (nominal, ordinal, etc.). Imputation for missing data will be considered if it is possible

[within an appropriate cutoff level (10%)] and empirically worth to do imputation of missing data.

Statistical analysis will be conducted by Bell Medical Solutions Inc. Tokyo, Japan in accordance with the Statistical Analysis Plan (SAP), provided by Amgen Astellas BioPharma K.K.

9.7.1 Planned Analyses

For the timely sharing of the collected data with PMDA and HCPs, analysis of interim data will be performed at the timing of J-PSUR. After the last patient enrolled to meet the expected sample size completes the observational period of 2 years (104 weeks), a data analysis will be performed and a final report summarizing the results of the survey will be completed shortly thereafter.

For both interim and final analyses, the PMS committee consisting of local external medical, pharmacovigilance, and statistical experts will review the survey analysis results. Involvement of the PMS committee in the review of PMS data and seeking expert advice on risk communication and other actions is customary in Japan.

9.7.1.1 Interim Analysis/Analyses

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

9.7.1.2 Primary Analysis

The primary analysis will be conducted after all the survey data are collected and cleaned.

Patient disposition, demographics and baseline characteristics will be summarized. Statistical test (chi-square, etc.) will be applied, depending on the type of variable (nominal, ordinal, etc.). See Sections 9.7.2.4 and 9.7.3 for analyses planned to address specified endpoints.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

In general, a descriptive analysis is conducted. Categorical variables are summarized with frequencies and percentage. Continuous variables are summarized with mean, standard deviation (SD), median, 1st Quartile (Q), and 3rd Q.

When statistical testing and inference are applied, two-sided p-value of <0.05 is considered significant and the 95% confidence interval (CI) is estimated. Adjustment for multiple comparisons is not considered.

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Participating investigators (physicians) and co-medicals are requested to make an effort to provide as complete information as possible through eCRFs.

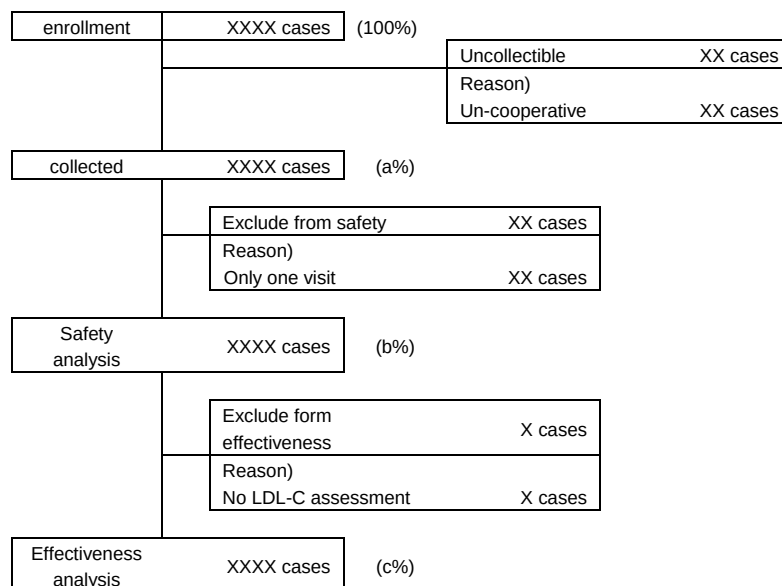
It is assumed that evolocumab prescriptions would typically be started and patients observed for the first few months at hospitals with experts of hypercholesterolemia and that some of patients would be transferred to general practice clinics resulting in loss-to-follow-up for the purpose of the survey. The rate of discontinuing evolocumab therapy and loss to follow-up (including that because of patients being transferred from specialized care to general practice) combined within 2 years from the first evolocumab prescription is estimated at about 50%. Because of the privacy law, continued follow-up of patients after they transfer to another medical institution is not feasible.

Imputation for missing data will be considered if it is possible [within an appropriate cutoff level (10%)] and empirically worth to do imputation of missing data.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

All enrolled patients will be summarized in the tree of patient disposition, as described below:



Percentage of a%, b% and c% (corresponding to enrollment) will be calculated.

9.7.2.3.2 Description of Patient Characteristics

Patient characteristics will be summarized for the following variables.

Patients demographic: sex, birth year/month, reason for usage (diagnosis: Familial Hypercholesterolemia [Heterozygous or Homozygous] and Hypercholesterolemia), height, weight, BMI, waist circumference, inpatient/outpatient, menopause, medical history of allergy, alcohol consumption, genetic test (for Familial Hypercholesterolemia [Heterozygous or Homozygous]), tendon xanthoma, skin tuberous xanthoma, duration of illness, medical history of coronary artery disease, diabetes mellitus/ impaired glucose intolerance, CKD, non-cardioembolic stroke, PAD, smoking (past, present), hypertension (systolic and diastolic blood pressure values), low HDL-C value (<40mg/dL), family history of premature coronary artery disease, other medical history (name of disease), HCV infection (negative, positive, amount of virus), dementia, other preexisting disease (name of disease), hepatic and renal dysfunction (grade, [see Appendix F]), pregnancy and lactation, concomitant medication of statin and other treatment for hypercholesterolemia, concomitant therapy of LDL-apheresis, non-medicine therapy (medical diet, therapeutic exercise), other concomitant medicine

9.7.2.4 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

Analysis for specified endpoints will be conducted as follows:

- Primary endpoint for safety:
Incidence (%), number of patients and number of events per 1,000 person-years with adverse drug reactions and serious adverse events during the observational period will be calculated and summarized (see Section 11.1 the definition of adverse event, serious adverse event, and other safety findings to be collected).
- Primary endpoint for effectiveness:
Percent change in LDL-C from baseline to 12W
- Secondary endpoints for safety:
Incidence (%), number of patients and number of events per 1,000 person-years with adverse drug reactions and serious adverse events in sub-population of patient characteristics, including the patient sub-populations specified as important missing information
- Secondary endpoints for effectiveness:
Percent change in LDL-C from baseline to 4W, 24W, 52W, 76W, and 104W
Absolute change in LDL-C from baseline to 4W, 12W, 24W, 52W, 76W, and 104W
Percent change in non-HDL-C, total cholesterol and triglycerides from baseline to 4W, 12W, 24W, 52W, 76W, and 104W.

9.7.2.5 Sensitivity Analysis

9.7.2.5.1 Subgroup Analysis

Sub-group analysis will be conducted by covariates as below:

- Patient demographics (e.g., age group, preexisting disease etc.)
- Medication status (e.g., dosage and duration of evolocumab therapy, concomitant medication for hypercholesterolemia)

9.7.2.5.2 Stratified Analysis

Incidence (%) of adverse drug reactions and serious adverse events will be summarized by the patients groups according to the LDL-C value: [REDACTED]

[REDACTED] Patients will be categorized by lowest LDL-C value during study.

9.7.2.5.3 Sensitivity Analysis for Residual Confounding and Bias

No sensitivity analysis is pre-planned.

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

See Section 9.7.2.4.

9.8 Quality Control

Quality control is conducted by checking whether data management operations were conducted based on the standard operation procedures of data management, and all results of quality control, including deviations and their measurements, are documented/reported and corrected deviations appropriately if they were found.

9.9 Limitations of the Research Methods

This is a prospective, observational cohort study, so it has a limitation of internal validity and strength of external validity in comparison with an interventional clinical study. Limitations common to this type of study, along with how to reduce errors, are summarized below.

Limitations	How to reduce errors
Missing and incomplete data are unavoidable, because there are some cases that data could not be collected at all evaluation time points, and some subjects could be lost to follow-up.	Efforts will be made to collect as complete data as possible through the use of EDC and instructions to investigators. After examining the extent of missingness and incompleteness of study data, an appropriate statistical data imputation method will be considered if it is possible [within an appropriate cutoff level (10%)] and empirically worth to do imputation of missing data.
Selection bias, information bias and confounding cannot be excluded.	Selection of participating medical institutions nationwide and enrollment of all-case FH patients who will receive evolocumab prescriptions at the eligible institutions as much as possible during enrollment period without exclusion criteria. Analysis results will be interpreted with caution, acknowledging the limitations, whether or not appropriate statistical methods could be applied to address the bias.

10. Protection of Human Subjects

The study protocol is reviewed and approved by the local regulatory agency, PMDA as well as IEC/IRB or external EC if not equipped in medical institutions. The study and data collection are conducted in accordance with the Pharmaceutical and Medical Device Act, GPSP and Helsinki Declaration. Local Medical Act provides the physician and co-medical 'Confidentiality Obligation' of patients that is set forth in the study agreement between the representatives of study site and Amgen Astellas BioPharma K.K.

Before registering the patient to this study, physician obtains the written informed consent from the patient after explanation of the aim, method, potential risk of the study and utilization of the patient's data in keeping individual patient's information unidentified.

11. Collection of Safety Information and Product Complaints

The external vendor in charge of day-to-day survey operation will check incoming safety information (adverse events, use in pregnant/lactating women) on EDC daily, and report the information to the Safety Department at Amgen Astellas BioPharma K.K. in accordance with standard operating procedures of Amgen Astellas BioPharma K.K.

11.1 Definition of Safety Events

11.1.1 Adverse Events

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

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

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

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

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate

instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

11.1.2 Serious Adverse Events

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

- is fatal
- is life threatening (places the patient 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 patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

11.1.3 Other Safety Findings

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

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

11.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic

by either Amgen Astellas BioPharma K.K. or by distributors and partners for whom Amgen Astellas BioPharma K.K. manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen Astellas BioPharma K.K. Drug(s) or device(s) includes investigational product.

Product complaints are collected separately from this survey in accordance with standard operating procedures of product complaints of Amgen Astellas BioPharma K.K.

11.2 Safety Reporting Requirements

The investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the investigator or reported by the patient that occur during observation study period (from first SC administration to last contact of study patient) are recorded in the patient's appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen Astellas BioPharma K.K. via the Safety Reporting Forms provided by the Safety Department of Amgen Astellas BioPharma K.K. within 24 hours of investigator'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 Astellas BioPharma K.K. via an Adverse Event Contingency Report Form within 24 hours of the investigator's awareness. When the first notification of an Adverse Event is reported to Amgen Astellas BioPharma K.K. 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 sample Safety Reporting Form, and Appendix E for sample Pregnancy and Lactation Notification Worksheets.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen Astellas BioPharma K.K. may amend the protocol at any time. If the protocol is amended, the Investigator has to follow amendments.

Amgen Astellas BioPharma K.K. reserves the right to terminate the study at any time.

13. Plans for Disseminating and Communicating Study Results

Communication material will be developed for HCPs for updating safety information and for the enlightenment of usage of evolocumab in a right way at the point of J-PSUR.

13.1 Publication Policy

The results of interim and final analyses will be submitted for publication as conference abstracts and/or medical journal articles.

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, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (e.g., manuscripts, abstracts, oral/slide presentations, book chapters) based on this survey must be reviewed through applicable company review processes at Amgen Astellas BioPharma K.K. and Amgen prior to submission.

14. Compensation

Participating institutions will receive payments for completing eCRFs and associated study-related activities. The amount of compensation will follow the standards set by Amgen Astellas BioPharma K.K. based on a fair market value assessment and local industry guideline. Compensation to the enrolled patients and their families in relation to health damage caused by adverse drug reactions in spite of proper use of drugs will be paid from the Japanese public relief system for sufferers from adverse drug reactions of any post marketed products, which is managed by the PMDA.

15. References

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http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/

16. Appendices

Appendix A. List of Stand-alone Documents

Not applicable.

Appendix B. ENCePP Checklist for Study Protocols

ENCEPP Checklist for Study Protocols (Revision 2)

Study title:

Long Term Post Marketing Specified Drug Use Result Survey for Evolocumab (AMG 145) in Japan (study number 20140409)

Study reference number:

20140409

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection ¹	☒	☐	☐	Page 9
1.1.2 End of data collection ²	☒	☐	☐	Page 9
1.1.3 Study progress report(s)	☒	☐	☐	Page 9,10
1.1.4 Interim progress report(s)	☒	☐	☐	Page 9
1.1.5 Registration in the EU PAS register	☒	☐	☐	Page 1
1.1.6 Final report of study results.	☒	☐	☐	Page 10

Comments:

1.1.3 Japanese periodic safety update report (J-PSUR)

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	Page 11
2.1.2 The objective(s) of the study?	☒	☐	☐	Page 11
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Page 12,13
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☒	☐	☐	Page 11
2.1.5 If applicable, that there is no <i>a priori</i> hypothesis?	☐	☐	☒	

Comments:

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

² Date from which the analytical dataset is completely available.

<u>Section 3: Study design</u>	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	Page 12
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	Page 20
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	Page 20

Comments:

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<u>Section 4: Source and study populations</u>	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	Page 12
4.2 Is the planned study population defined in terms of:	☒	☐	☐	Page 12
4.2.1 Study time period?	☒	☐	☐	Page 14
4.2.2 Age and sex?	☒	☐	☐	Page 12
4.2.3 Country of origin?	☒	☐	☐	Page 12,13
4.2.4 Disease/indication?	☒	☐	☐	Page 14
4.2.5 Co-morbidity?	☐	☐	☒	
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	Page 13

Comments:

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<u>Section 5: Exposure definition and measurement</u>	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	Page 14,15
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☒	☐	☐	Page 15
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?	☐	☐	☒	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☐	☐	☒	

Comments:

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<u>Section 6: Endpoint definition and measurement</u>	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	Page 14
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	Page 15

Comments:

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

Comments:

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<u>Section 8: Data sources</u>	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:	☒	☐	☐	Page 15
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	Page 15
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	Page 15
8.1.3 Covariates?				

8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	Page 15
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Page 15
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	Page 15
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☐	☒	☐	
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	☐	☒	☐	
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☒	☐	
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

All adverse events are encoded by MedDRA under regulatory (PMDA) requirement.

<u>Section 9: Study size and power</u>	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	Page 15

Comments:

<u>Section 10: Analysis plan</u>	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☐	☒	☐	
10.2 Is the choice of statistical techniques described?	☒	☐	☐	Page 17
10.3 Are descriptive analyses included?	☒	☐	☐	Page 18,19
10.4 Are stratified analyses included?	☒	☐	☐	Page 20
10.5 Does the plan describe methods for adjusting for confounding?	☐	☐	☒	
10.6 Does the plan describe methods addressing effect modification?	☐	☐	☒	

Comments:

<u>Section 11: Data management and quality control</u>	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	Page 21
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	Page 16
11.3 Are methods of quality assurance described?	☒	☐	☐	Page 21
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	Page 21
11.5 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

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<u>Section 12: Limitations</u>	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss:				
12.1.1 Selection biases?	☒	☐	☐	Page 21
12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	Page 21
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	Page 15,16
12.3 Does the protocol address other limitations?	☒	☐	☐	Page 21

Comments:

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<u>Section 13: Ethical issues</u>	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	Page 22
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	Page 22
13.3 Have data protection requirements been described?	☒	☐	☐	Page 22

Comments:

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<u>Section 14: Amendments and deviations</u>	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	Page 24,25

Comments:

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<u>Section 15: Plans for communication of study results</u>	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	Page 9
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Page 25

Comments:

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Name of the main author of the protocol: _____

Date: 25/5/2016

Signature: _____

Appendix C. Sample Safety Reporting Form(s)

Project ID: 20140409 Subject ID:	AMGEN	Safety Reporting Form Primary Data Collection	Date of Report:
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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					
address		address							
city		state/province		city					
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)				
country				☐ F ☐ M	Was consent obtained to follow-up with HCP?				
address					☐ Yes ☐ No				
city		state/province	postal code	Weight	Height				
phone		fax		☐ lbs ☐ kg	☐ in ☐ cm				
				Race	Is patient also reporter?				
					☐ Yes ☐ No				
6. Medical History (include primary diagnosis)			7. Suspect Product Information (include dosing details)						
			Product: _____						
			Indication: _____						
			Start Date	Stop Date	Dose				
			day month year	day month year					
					Route				
					Freq				
Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No			Prefilled Syringe? ☐ Yes ☐ No	Lot #	Vial size				
Allergy: _____			Other Device _____	☐ Unknown					
				Serial #					
				☐ Unavailable / Unknown					
8. AE, other safety finding, or product complaint information					HCP ONLY				
Finding (List main event first; one event per line)	Onset Date	Resolved Date	Hospitalization		Serious Criteria	Action Taken	Outcome	Severity	Relationship to Product/ Device
		(If patient died, list date of death) Cause of Death: (provide autopsy report)	Admitting dx (provide discharge summary) Date Admitted Date Discharged	Hospitalized? ☐ Yes ☐ No Prolonged? ☐ Yes ☐ No					
	day month year	day month year	day month year	day month year	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	1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=Drug challenge (state outcome)	1=resolved 2=resolved w/ sequelae 3=resolving	1=mild 2=moderate 3=severe	Is there a reasonable possibility that this event may have been caused by the Product / Device?
									Product Device
									Y N Y N
									Y N Y N
									Y N Y N
9. Description: chronological summary of symptoms or product complaint from above (signs, diagnosis, treatment, concomitant medications including those used to treat event.)									

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

Not applicable.

Appendix E. Pregnancy and Lactation Notification Worksheets

AMGEN[®] Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

1. Case Administrative Information

Protocol/Study Number: _____

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: _____

Print Form

AMGEN[®] Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

SELECT OR TYPE IN A FAX#

enter fax number

1. Case Administrative Information

Protocol/Study Number: _____

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: _____

Appendix F. Hepatic and renal impairment as reference grade

	grade		
Hepatic impairment	mild	moderate	severe
AST(GOT) ALT(GPT)	>1 - 3 x ULN	>3 - 5 x ULN	>5 x ULN
Serum bilirubin	>1 -1.5 x ULN	>1.5 - 3 x ULN	>3 x ULN
Renal impairment	mild	moderate	severe
Serum creatinine	>1 -1.5 x ULN	>1.5 - 3 x ULN	>3 x ULN

ULN: upper limit of normal

Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (Ver. 4.03: Jun 14, 2010)