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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Date of last version of the protocol	08 April 2016
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Product Reference	
Procedure Number	
Marketing Authorisation Holder(s)	Amgen Astellas Biopharma K.K.
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
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Marketing Authorisation Holder

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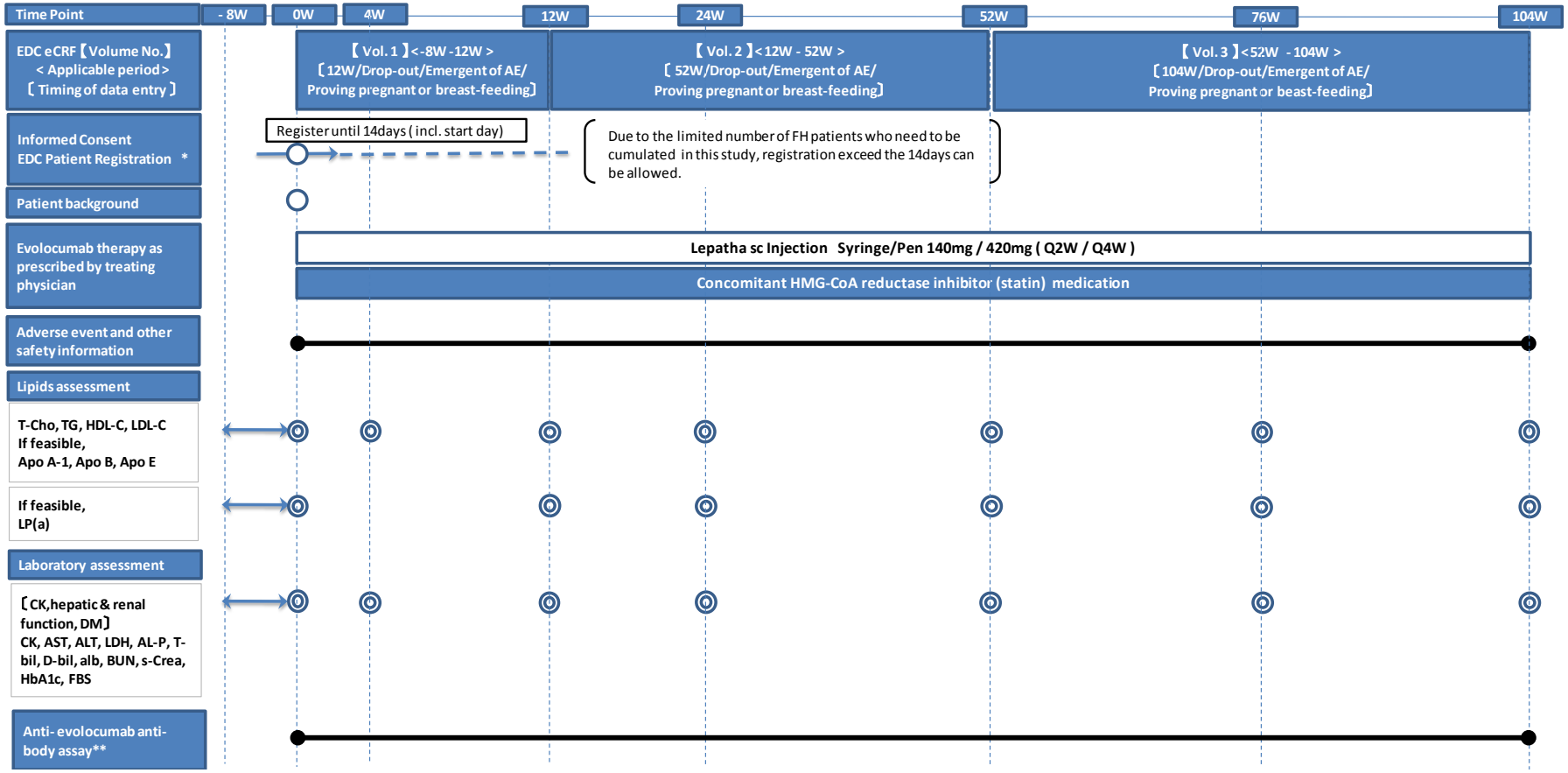
Study Design Schema



*) 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.

1. Table of Contents

Summary Table of Study Protocol 1

Study Design Schema 2

1. Table of Contents 3

2. List of Abbreviations 6

3. Responsible Parties 7

4. Abstract 7

5. Amendments and Updates 9

6. Milestones 9

7. Rationale and Background 10
   - 7.1 Diseases and Therapeutic Area 10
   - 7.2 Rationale 11
   - 7.3 Statistical Inference (Estimation or Hypothesis [es]) 11

8. Research Question and Objectives 11
   - 8.1 Primary 11

9. Research Methods 12
   - 9.1 Study Design 12
   - 9.2 Setting and Study Population 12
     - 9.2.1 Study Period 12
     - 9.2.2 Selection and Number of Sites 12
     - 9.2.3 Patient/Healthcare Professional Eligibility 13
     - 9.2.4 Matching 13
     - 9.2.5 Baseline Period 13
     - 9.2.6 Study Follow-up 13
   - 9.3 Variables 13
     - 9.3.1 Exposure Assessment 14
     - 9.3.2 Outcome Assessment 14
     - 9.3.3 Covariate Assessment 14
     - 9.3.4 Validity and Reliability 15
   - 9.4 Data Sources 15
   - 9.5 Study Size 15
   - 9.6 Data Management 16
     - 9.6.1 Obtaining Data Files 16
     - 9.6.2 Linking Data Files 16
     - 9.6.3 Review and Verification of Data Quality 16
   - 9.7 Data Analysis 16

9.7.1 Planned Analyses ... 17
9.7.2 Planned Method of Analysis ... 18
9.7.3 Analysis of Safety Endpoint(s)/Outcome(s) ... 21
9.8 Quality Control ... 21
9.9 Limitations of the Research Methods ... 21

10. Protection of Human Subjects ... 22

11. Collection of Safety Information and Product Complaints ... 22
11.1 Definition of Safety Events ... 22
11.1.1 Adverse Events ... 22
11.1.2 Serious Adverse Events ... 23
11.1.3 Other Safety Findings ... 23
11.1.4 Product Complaints ... 23
11.2 Safety Reporting Requirements ... 24

12. Administrative and Legal Obligations ... 24
12.1 Protocol Amendments and Study Termination ... 24

13. Plans for Disseminating and Communicating Study Results ... 24
13.1 Publication Policy ... 25

14. Compensation ... 25

15. References ... 26

16. Appendices ... 28

List of Tables

List of Figures

List of Appendices

Appendix A. List of Stand-alone Documents 29
Appendix B. ENCePP Checklist for Study Protocols 30
Appendix C. Sample Safety Reporting Form(s) 31
Appendix D. Additional Safety Reporting Information 32
Appendix E. Pregnancy and Lactation Notification Worksheets 33
Appendix F. Hepatic and renal impairement as reference grade 35

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):

Bell Medical Solutions Inc., Japan

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. The proposed post-marketing survey will provide descriptive data from the real-world use of evolocumab in patients in Japan to supplement the data in the J-NDA. Japan Risk Management Plan (J-RMP) includes this survey as a part of post-marketing pharmacovigilance activities.

- 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

For the timely sharing of the collected data with PMDA and Health care professionals (HCPs), analysis of interim data will be performed at the timing of Japan periodic safety update report (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 by planned date as below.

For both interim and final analyses, the post marketing surveillance (PMS) committee consisting of local medical, pharmacovigilance, and statistical experts will review the survey analysis results and provide advice on risk communication and other actions.

No stopping rules will be applied to this non-interventional survey.

Milestone	Planned date (*:data lock point)
Start of data collection	June 2016
End of data collection	April 2020
J-PSUR No. 1	July 2016*
J-RMP milestone at the end of early phase post-marketing vigilance (EPPV)	October 2016*
J-PSUR No. 2	January 2017*
J-PSUR No. 3	July 2017*
J-PSUR No. 4	January 2018*
Interim report of survey results	January 2018*

J-PSUR No. 5	January 2019*
J-PSUR No. 6	January 2020*
J-PSUR No. 7	January 2021*
J-PSUR No. 8	January 2022*
J-PSUR No. 9	January 2023*
Finial report of survey results	April 2023
Submission of the re-examination dossier	April 2024

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Cardiovascular disease (CVD) is the leading cause of death and disability in both the developed and developing worlds and is responsible for over 10% of the global total disease burden among all major disease, injuries, and risk factors that impact mortality (WHO, 2011).Elevated LDL-C is a major modifiable risk factor for the development of CVD and is a validated surrogate endpoint for cardiovascular risk reduction. Data from interventional and epidemiologic studies show that, at a population level, LDL-C is a strong independent predictor of Coronary Heart Disease risk across diverse patient populations (The Emerging Risk Factors Collaboration, 2009; CTTC, 2010; Robinson et al, 2005), including Japanese populations (Okamura 2003; Matsuzaki 2002; Mabuchi 2002). Studies of genetic variants (both gain of function and loss of function) provide additional evidence supporting LDL-C as a therapeutic target and surrogate for cardiovascular outcomes (Cohen et al, 2006; Abifadel et al, 2003).

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

In 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 (52 weeks) were presented. The proposed post-marketing survey will provide descriptive data from the real-world use of evolocumab in patients in Japan to supplement the data in the J-NDA. J-RMP includes this survey as a part of post-marketing pharmacovigilance activities.

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.

<Safety specification items to focus, as described in J-RMP>

(1) Important Identified Risks
None

(2) Important Potential Risks
Hypersensitivity, Immunogenicity

(3) Important Missing Information, used cases as follows;

Use in Homozygous Familial Hypercholesterolemia (including pediatrics), elderly (≥75 years), hepatic impairment [see Appendix F]), infected hepatitis C, long-term use including effects of persistent LDL-C level < 40 mg/dL

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 14days 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 1500 nation-wide medical institutions equipped with department of lipid metabolism, circulation, diabetes, endocrinology, others (neurology, brain surgery) and 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 2years 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.

<u>Patient information for registration:</u> 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)

<u>Patient demographics and medical history</u>: 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, chronical 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

There will be interim analyses to support safety reporting and assessments of effectiveness endpoints.

Under regulatory requirement, periodical analyses will be conducted in a timeline aligned to J-PSUR (every 6 months for the first 2 years and annually thereafter until re-examination). The interim result will be reported as a part of J-PSUR.

As planned milestone activity of J-RMP, the interim analysis (e.g. listing of adverse events) will be implemented at the end of Early Postmarketing Phase Vigilance (EPPV: 6 months after the product launch).

An additional interim analysis will be conducted when data become available for 1000 patients having the Week 12 of evolocumab administration or ended the scheduled follow-up. The result of the analysis will used for the purpose of sharing the safety information with HCPs in a timely manner.

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.

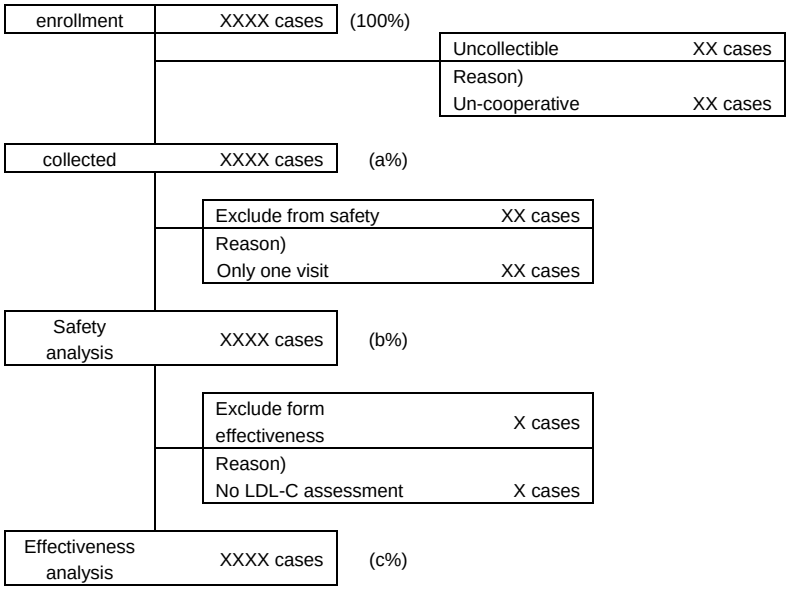
It is assumed that evolocumab prescriptions would typically be started and patients observed for the first few months at hospitals with experts of hypercholesterolemia and that some of patients would be transferred to general practice clinics resulting in loss-to-follow-up for the purpose of the survey. 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: (a) ≥40mg/dL, (b) ≥25mg/dL, <40 mg/dL and (c) <25mg/dL. 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 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.

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16. Appendices

Appendix A. List of Stand-alone Documents

Not applicable.

Appendix B. ENCePP Checklist for Study Protocols

[Delete this Appendix if not a PASS study.]

A copy of the the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Checklist for study protocols is available at the following location: http://www.encepp.eu/standards_and_guidances/index.html. It is to be completed and signed by the main author of the study protocol and should be included in Appendix B.

The checklist will facilitate the review of the protocol and evaluation of whether investigators have considered important methodological aspects.

In question 9.5 of the Checklist Revision 1:

"Study start" means "Start of data collection"

"Study progress" means "Progress Report(s)"

"Study completion" means "End of data collection"

"Reporting" means "final report of the study results"

Appendix C. Sample Safety Reporting Form(s)

Project ID: 20140409 Subject ID:	AMGEN	**Safety Reporting Form** Primary Data Collection	Date of Report:

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* ☐ F ☐ M	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?* ☐ Yes ☐ No
country						
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	Prefilled Syringe? ☐ Yes ☐ No	Lot # _____ ☐ Unknown	Vial size
Allergy: _____	Other Device _____	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 (day month year)	Resolved Date (day month year) (If patient died, list date of death) Cause of Death: _____ (provide autopsy report)	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? 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:____________________________________

____

____

<u>**Form Completed by**</u>:

Print Name: ____________________________________ **Title:** ____________________________________

Signature: ____________________________________ **Date:** ____________________________________

****

Effective Date: March 27, 2011 Page **1** of **1**

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:** _____

****

Effective Date: 03 April 2012, version 2. Page **1** of **1**

Appendix F. Hepatic and renal impairement as reference grade

	grade		
Hepatic impairement	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 impairement	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)