Summary Table of Study Protocol

Title	An Observational Case Series to Describe Women Exposed to Repatha During Pregnancy and Infant Outcomes During the First Year of Life
Protocol version identifier	20200408, 1.0
Date of last version of the protocol	03 March 2021
EU Post Authorization Study (PAS) Register No	TBD (Registration will occur after approval of the protocol and prior to commencement of first data capture)
Active Substance	Evolocumab
Medicinal Product	Repatha
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	Yes
Research Question and Objectives	Among women exposed to Repatha during pregnancy, to estimate the proportion of: - pregnancy and maternal complications - adverse events in the developing fetus and neonate - and among their infants, adverse events for the first year of life.
Country(ies) of Study	Global

Author	PPD, Manager, Observational Research, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD PPD, Director, Observational Research, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD PPD, Director, Global Safety, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD PPD, Director, Regulatory Affairs, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD PPD, Medical Director, Clinical Research, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc.
MAH Contact	PPD, Regulatory Affairs Manager, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD

This protocol was developed, reviewed, and approved in accordance with Amgen's standard operating procedures.

Confidentiality Notice

This document contains confidential information of Amgen Inc.

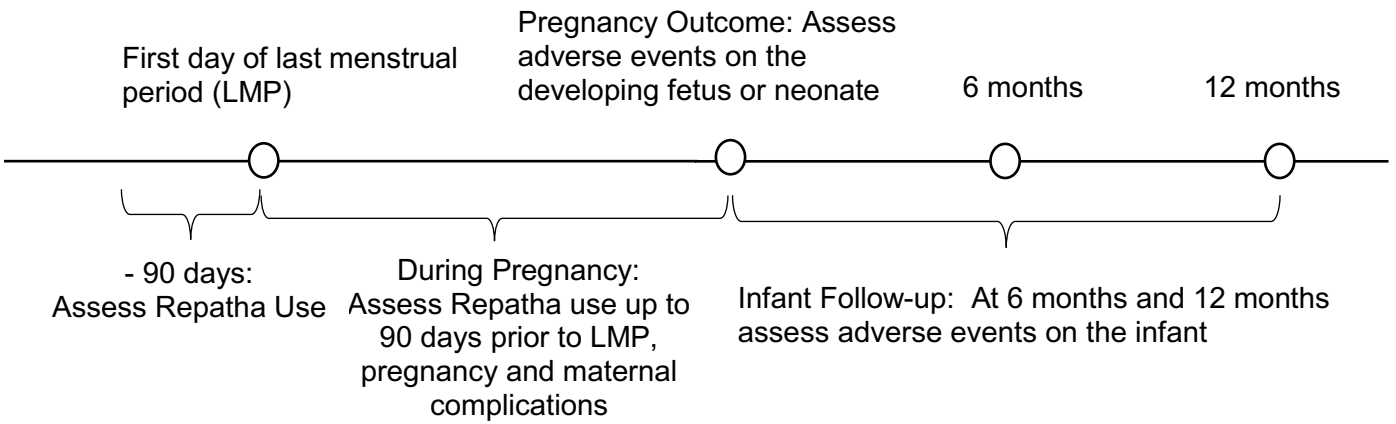
This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

The information in this document cannot be used for any purpose other than the evaluation or conduct of the research without the prior written consent of Amgen Inc.

If you have questions regarding how this document may be used or shared, call the Amgen Medical Information number: Amgen's general number in the US (1-805-447-1000).

Study Design Schema

Study Period: July 2015 – July 2025



Case finding through the Amgen Global Safety Database and other post marketing sources which include: spontaneous (including regulatory authority and literature), solicited (ie, patient support programs and market research), and postmarketing non-interventional studies.

Index date: Later date of first day of LMP or first date of Repatha use

1. Table of Contents

List of Appendices

2. List of Abbreviations

Acronym	Definition
AGS	Amgen Global Safety
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDA	Food and Drug Administration
HCP	Healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
HeFH	Heterozygous Familial Hypercholesterolemia
HoFH	Homozygous Familial Hypercholesterolemia
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LDL	Low-Density Lipoprotein
LDL-C	Low-Density Lipoprotein Cholesterol
LMP	Last menstrual period
MAH	Marketing Application Holder
MI	Myocardial Infarction
OTC	Over the counter
PASS	Post-authorisation safety study
PCSK9	Proprotein Convertase Subtilisin Kexin type 9
PCSK9i	Proprotein Convertase Subtilisin Kexin type 9 inhibitor
US	United States
USPI	United States Prescribing Information

3. Responsible Parties

PPD , PhD, MPH, Amgen Inc.

PPD , PhD, MPH, Amgen Inc.

PPD , RN, Amgen Inc.

PPD , MS, RAC, Amgen Inc.

PPD , MD, Amgen Inc.

4. Abstract

- Study Title

An Observational Case Series to Describe Women Exposed to Repatha During Pregnancy and Infant Outcomes During the First Year of Life

- Study Background and Rationale

Repatha is a proprotein convertase subtilisin kexin type 9 inhibitor (PCSK9i) antibody indicated to (1) reduce the risk of myocardial infarction (MI), stroke and coronary revascularization in adults with established cardiovascular disease (2) as an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for treatment of adults with primary hyperlipidemia (including heterozygous familial hypercholesterolemia [HeFH]) to reduce low-density lipoprotein cholesterol (LDL-C) and (3) as an adjunct to diet and other LDL-C lowering therapies in patients with homozygous familial hypercholesterolemia (HoFH) who require additional lowering of LDL-C.

This study is being conducted to address a Food and Drug Administration (FDA) postmarketing requirement to conduct a single-arm prospective and retrospective observational study of pregnant women exposed to Repatha to evaluate fetal and infant outcomes through the first year of life. This study will estimate the proportion of pregnancy and maternal complications, adverse events in the developing fetus and neonate, and adverse events in the infant through the first year of life using data from pre-existing reports within Amgen's Global Safety Database.

- Research Question and Objective(s)

Objectives	Endpoints
Primary	
Among women exposed to Repatha during pregnancy, to estimate the proportion of: - Pregnancy and maternal complications - Adverse events in the developing fetus and neonate - And among their infants, adverse events for the first year of life.	• Number of cases reporting pregnancy and maternal complications. • Pregnancy Outcomes: Number of cases reporting live full-term births, spontaneous abortion, elective abortion, stillbirth, and premature delivery. • Infant Outcomes: Number of cases reporting adverse events including complications, medical problems or congenital anomalies at birth. • Number of cases reporting adverse events at 6 months and 12 months.

- Hypothesis(es)/Estimation

This is an estimation study. No formal hypothesis will be tested.

- Study Design/Type

This is a Global prospective and retrospective observational case series of pregnant women exposed to Repatha during pregnancy and their infants through the first year of life.

- Study Population or Data Resource

Case finding through the Amgen Global Safety Database and other post marketing sources which include: spontaneous (including regulatory authority and literature), solicited (ie, patient support programs and market research), and postmarketing non-interventional studies. Retrospectively, data will be extracted from pre-existing postmarketing reports obtained from Amgen's Global Safety Database for women exposed to Repatha during pregnancy and their infants between July 2015 and the approval date of this protocol. Prospectively, from approval date of this protocol through July 2025, secondary data from postmarketing reports will be analyzed for women who have been exposed to Repatha during their pregnancy and their infants. Patients who refused consent will be excluded.

- Summary of Patient Eligibility Criteria

Women exposed to Repatha during pregnancy and their infants through the first year of life who consent to provide their information to Amgen.

- Follow-up

If the pregnant women consent for follow-up, then Amgen will follow-up with the pregnant women from the time they are exposed to Repatha through the pregnancy outcome and their infants will be followed through the first year of life.

- Variables

Outcome Variable(s): The outcomes for the study include occurrence and dates of pregnancy and maternal complications, pregnancy outcomes, and infant outcomes based on self-report. Pregnancy outcomes include the number of cases reporting live full-term births, spontaneous abortion, elective abortion, fetal death/stillbirth, and premature delivery. Infant outcomes are the number of cases reporting adverse events including complications, medical problems or congenital anomalies at birth and the number of cases reporting adverse events at 6 months and 12 months which may include whether they have not followed growth curves or met development milestones as expected for chronological age.

Exposure Variable(s): The period defining exposure to Repatha during pregnancy will be any number of days, at any dose, and at any time from up to 90 days pre-LMP, through the first day of the last menstrual period (LMP) and up to and including the end of pregnancy. Identification of pregnancy will be via postmarketed reporting through Amgen's Global Safety Database.

Other Covariate(s): Other covariates will be included which pertain to maternal information, exposure and pregnancy and delivery. Maternal covariates include demographic information for the mother, pregnancy history; medical history; other relevant history that may impact the pregnancy (family history, mother's occupation). Variables related to exposure include current medication and dates of use (prescription and over-the-counter [OTC]); and occurrence and dates of current pregnancy complications. Characteristics of pregnancy and delivery such as maternal conditions, birth information, delivery details, and newborn complications.

- Study Sample Size

Sample size will not be pre-determined. This is a descriptive study which will identify the number of pregnant women exposed to Repatha through the Amgen Global Safety Database.

- Data Analysis

These cases constitute an exposed case series, thus line listings of pregnancy and maternal complications, pregnancy outcomes, infant outcomes and adverse events will be summarized along with tabulations of the numbers and frequencies of events by category of report: numbers who did not provide consent for follow-up, timing of exposure (pre-LMP, which trimester), and indication for use of the medication. Collection of exposure and outcome information in this group provides additional evidence on the safety of Repatha use during pregnancy. The denominator is the number of pregnant women exposed to Repatha during pregnancy and the numerator is the number with the outcome. The proportion at birth with adverse events including complications, medical problems or congenital anomalies will be estimated in infants of women exposed to Repatha during pregnancy. The proportion of infants with adverse events observed at 6 months and 12 months of age will be estimated. The proportion of mothers who have received Repatha at any time during the pregnancy with pregnancy and maternal complications and adverse events will be summarized. Corresponding 95% confidence intervals will also be presented.

To assess effects on the developing fetus and neonate in women exposed to Repatha during pregnancy, the proportion with spontaneous abortions, elective abortions, fetal deaths/stillbirths and premature delivery will be presented, along with corresponding 95% confidence intervals

If the available safety information relevant to exposure during pregnancy represents a safety signal, the signal will be further evaluated through the Amgen safety governance structure and, if deemed necessary, escalated for consideration of changes to the Reference Safety Information (eg, United States Prescribing Information [USPI]) as well as other forms of risk communication (eg, Dear Healthcare Provider Letters).

5. Amendments and Updates

None.

6. Rationale and Background

In the United States (US), Repatha is indicated: (1) In adults with established cardiovascular disease to reduce the risk of MI, stroke, and coronary revascularization; (2) As an adjunct to diet, alone or in combination with other lipid-lowering therapies (eg, statins, ezetimibe), for the treatment of adults with primary hyperlipidemia (including HeFH) to reduce LDL-C; and (3) as an adjunct to diet and other LDL-C-lowering

therapies (eg, statins, ezetimibe, low-density lipoprotein (LDL) apheresis) for the treatment of patients with HoFH who require additional lowering of LDL-C (revised USPI, February 2019). There are no data available on use of Repatha in pregnant women to inform a drug-associated risk. In Section 8.1, the USPI for Repatha states to "consider the benefits and risks of REPATHA and possible risks to the fetus before prescribing REPATHA to pregnant women." Information on the pregnancy exposure registry was added to Section 8.1 of the USPI as well as to the US Patient Package Insert (February 2019).

6.1 Diseases and Therapeutic Area

A serine protease expressed predominantly in the liver, kidney, and intestine (Seidah et al, 2003), proprotein convertase subtilisin kexin type 9 (PCSK9), plays an important role in the recycling and regulation of the LDL receptor (Horton et al, 2007; Brown and Goldstein, 2006). PCSK9 acts via direct binding to the LDL receptor, resulting in post-translational down-regulation of receptor expression on the hepatic cell surface. This in turn leads to increased levels of circulating LDL-C. Repatha is a fully human monoclonal IgG2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with the LDL receptor, thus lowering plasma LDL-C levels.

Based on modality, mechanism of action, published human data, and nonclinical studies, safety issues during pregnancy are not expected with Repatha exposure. As a therapeutic monoclonal antibody, placental transfer during organogenesis in humans is likely to be low (DeSesso et al, 2012; ICH, 2009). Further, the conceptus derives at least 80% of its cholesterol needs from endogenous synthesis rather than from the maternal circulation (Bartels et al, 2012; Woollett, 2005). Independence from maternal sterol status indicates that normal fetal development would not be expected to be affected by the cholesterol lowering properties of Repatha which are independent of effects on cholesterol synthesis. Across multiple species including humans, the rates of cholesterol synthesis in the fetus are much greater than in the adult (Dietschy et al, 1993). Consistent with this, low maternal cholesterol is not causally associated with adverse birth outcomes. Whether mediated by dietary intervention or by genetic mutations, normal embryo-fetal development has been observed in children born to mothers with low cholesterol throughout pregnancy (Homanics et al, 1993; McMurry et al, 1981; Connor et al, 1978).

Moreover, in animal and reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were subcutaneously administered Repatha

from organogenesis through parturition at exposures up to 12 times the exposure at the maximal recommended human dose of 420 mg every month. However, in a similar study with another drug in the PCSK9 inhibitor antibody class, humoral immune suppression was observed in infant monkeys exposed to that drug in utero at all doses. The exposures where immune suppression occurred in infant monkeys were greater than those expected clinically. No assessment for immune suppression was conducted with Repatha in infant monkeys (Amgen, 2016).

6.2 Rationale

This study is being conducted to address a FDA postmarketing requirement to conduct a prospective and retrospective observational study of pregnant women exposed to Repatha to evaluate fetal and infant outcomes through the first year of life. This study will estimate the risk of pregnancy and maternal complications, adverse events on the developing fetus and neonate, and adverse events on the infant through the first year of life using data from pre-existing reports within Amgen's Global Safety Database.

6.3 Statistical Inference (Estimation or Hypothesis)

This is an estimation study. No formal hypothesis will be tested.

7. Research Question and Objectives

7.1 Primary

Among women exposed to Repatha during pregnancy, to estimate the proportion of:

1. Pregnancy and maternal complications
2. Adverse events in the developing fetus and neonate
3. And among their infants, adverse events for the first year of life.

8. Research Methods

8.1 Study Design

This is a worldwide, single-arm, observational case series that collects prospective and retrospective data in women exposed to Repatha during pregnancy to estimate the proportion of pregnancy and maternal complications, adverse events in the developing fetus and neonate, and adverse events in the infant in all exposed pregnancies. Infant outcomes will be assessed through the first year of life.

8.2 Setting and Study Population

The study population includes women worldwide exposed to Repatha during pregnancy that consented for pregnancy and infant follow-up. Case information will be obtained through the Amgen Global Safety Database and other post marketing sources which

include: spontaneous (including regulatory authority and literature), solicited (ie, patient support programs and market research), and postmarketing non-interventional studies.

8.2.1 Study Period

The study is retrospective and prospective. Retrospectively, data will be extracted from pre-existing postmarketing reports obtained from Amgen's Global Safety Database for women exposed to Repatha during pregnancy and their infants between July 2015 and the approval date of this protocol. Prospectively, from approval date of this protocol through July 2025, secondary data from postmarketing reports will be analyzed for women who have been exposed to Repatha during their pregnancy and among their infants.

8.2.2 Patient Eligibility

8.2.2.1 Inclusion Criteria

Women exposed to Repatha during pregnancy and their infants through the first year of life who consent to provide their information to Amgen.

8.2.2.2 Exclusion Criteria

None.

8.2.3 Matching

Not applicable.

8.2.4 Baseline Period

This study has no formal baseline period. Pregnant women exposed to Repatha for any number of days, at any dose, and at any time from up to 90 days prior to the LMP and up to and including the end of pregnancy will be identified through Amgen's Global Safety Database and other post marketing sources which include: spontaneous (including regulatory authority and literature), solicited (ie, patient support programs and market research), and postmarketing non-interventional studies.

8.2.5 Study Follow-up

If pregnant women consent, they will be followed from the later date of the first day of their LMP or the date of their exposure to Repatha (index date) through the pregnancy and birth. A postpartum follow-up will occur approximately 6 to 8 weeks after delivery. Additional follow-up will occur when the infant is 6 and 12 months of age.

8.3 Variables

8.3.1 Exposure Assessment

The period defining exposure to Repatha during pregnancy will be any number of days, at any dose, and at any time from 90 days prior to the first day of the LMP up to and including the end of pregnancy. Identification of pregnancy will be via postmarketed reporting through Amgen's Global Safety Database.

8.3.2 Outcome Assessment

Pregnancy outcomes include the number of women reporting pregnancy or maternal complications, as well as, the number reporting:

- Live full-term births
- Spontaneous abortion defined as non-deliberate fetal death which occurs prior to 20 completed weeks post-LMP
- Elective abortion defined as deliberate termination of pregnancy at any time in gestation
- Fetal death/Stillbirth defined as non-deliberate fetal death anytime in gestation at or after 20 completed weeks post-LMP
- Premature delivery defined as live birth prior to 37 weeks gestation as counted from LMP (eg, ultrasound adjusted date or Ballard's score)

Outcomes related to pregnancy and maternal complications will be assessed with a Pregnancy Questionnaire (a sample form included in Appendix C). Outcomes for live births will be assessed with a Post Due Date Questionnaire (a sample form included in Appendix D) from the Amgen Global Safety Database.

The number of infants with adverse events including complications, medical problems or congenital anomalies at birth will be assessed with a Post Due Date Questionnaire (a sample form included in Appendix D) from the Amgen Global Safety Database.

Major malformations or birth defects are defined as abnormalities incompatible with life or requiring medical/ surgical intervention. The term minor birth defect generally refers to minor physical anomalies with less clinical importance that represent deviations from what is considered normal and do not have obvious medical, surgical, or cosmetic consequences. Major birth defects identified up to 1 year of age by the mother or the healthcare provider will be included in the primary analysis. Major structural birth defects may be reported by the mother, a family member or her or her child's HCP via medical records. If a major malformation is reported the medical record will be adjudicated by a physician with expertise in teratology, pediatrics, and dysmorphology. Defects will be

classified using the Center for Disease Controls (CDC) criteria (CDC 2017.: https://www.cdc.gov/ncbddd/birthdefects/macdp.html).

Infant outcomes are the number of cases reporting adverse events at 6 months and 12 months and may include whether they have not followed growth curves or met development milestones as expected for chronological age. These outcomes will be assessed with an Infant Questionnaire (a sample form included in Appendix E).

8.3.3 Covariate Assessment

8.3.3.1 Pregnancy Information

Variables related to pregnancy such as demographics (age); pregnancy history; medical history; current medication and dates of use (prescription and OTC); other relevant history (family history, mother's occupation), and occurrence and dates of pregnancy complications.

8.3.3.2 Post Due Date Birth Information

Variables related to pregnancy and delivery such as maternal conditions, newborn complications, birth information, and delivery details.

8.3.4 Validity and Reliability

The primary exposure variable of exposure during pregnancy is based on maternal, other family member, or HCP report. The outcome variable of adverse events at birth including complications, medical problems or congenital anomalies is based on maternal or HCP report. Adverse events reported at 6 months and 12 months are based on follow-up received from the pregnant woman or HCP. For other outcome variables, standard methods are used to classify the outcome, confirm reliability of data capture, data entry and classification.

8.4 Data Sources

The Amgen Global Safety Database is a comprehensive pharmacovigilance database that contains reports of adverse event data for all Amgen products including Repatha and all safety reports from clinical and post market sources. Amgen performs follow-up on adverse events reported for all products including Repatha as per Amgen's due diligence process. The Amgen Global Safety Database includes reports of pregnancy, birth outcome, and infant health information of women who have had direct exposure to Repatha prior to or during pregnancy. Pregnant women may or may not provide consent for their health and their children's health information to be obtained by Amgen. The database contains positive and negative pregnancy outcome data, including congenital

anomalies, spontaneous and elective abortions, fetal death/stillbirths, and premature birth.

All Repatha pregnancy cases (which may include multiple pregnancies from the same woman), of which Amgen becomes aware, reported from the postmarketing experience (including through spontaneous reporting, cases solicited through patient support programs, market research, from the literature, from regulatory authorities, or postmarketing non-interventional studies) are entered into the Amgen Global Safety Database. Pregnancy exposure case reporting and follow-up through the infant's first year of life is voluntary and participants are free to withdraw at any time.

Amgen does not provide compensation for participation in the follow-up process. Participants are required to provide verbal or written consent that allows Amgen to collect relevant pregnancy, birth outcome, and infant health information.

As per Amgen's due diligence process, upon notification of a Repatha exposure during pregnancy (with or without an adverse event), Amgen Global Patient Safety follows up with the reporter to request informed consent to obtain pregnancy and infant health information from the mother. Follow-up will be performed as per Amgen's routine pharmacovigilance process at predefined intervals and adjusted accordingly depending on whether the mother is pregnant or has already delivered. Information requested may include, but is not limited to, alternate contact information for the mother, such as contact information of a close relative or friend, pregnancy/delivery details, medical history, laboratory and diagnostic tests, and HCP names. The process includes a set number of follow-up attempts over predefined intervals (post birth, when the infant is 6 months and 12 months). If there is no response to the follow-up attempts the due diligence process is complete and the case is considered lost to follow-up. An exception to this process is when the reporter explicitly states they are not prepared to provide any further information, did not provide consent to follow-up, or refused to provide any additional information about the pregnancy or infant. If this occurs, follow-up is not conducted.

8.5 Study Size

This is an estimation study. The study size will depend on the number of reports submitted to the Amgen Global Safety Database for women exposed to Repatha during pregnancy.

8.6 Data Management

As per Amgen's due diligence process, hard copy questionnaire forms are mailed to women exposed to Repatha who have provided consent. Completed forms may be mailed, faxed, or emailed back to Amgen Global Safety (AGS). The forms are processed in the Amgen Global Safety Database in accordance with Amgen policies, processes and practices. Attempts to obtain additional information are performed if consent is provided. If further details are made available to Amgen, the Amgen Global Safety Database is updated.

8.7 Data Analysis

8.7.1 Planned Analyses

8.7.1.1 Interim Analysis/Analyses

Annual interim reports of analyses performed during the study will be submitted to the FDA.

8.7.1.2 Primary Analysis

The primary analysis for both annual reports and final analysis (at the end of the study) describes the approach to summarize primary outcomes.

8.7.2 Planned Method of Analysis

8.7.2.1 General Considerations

The analysis of this exposed case series will be descriptive only.

8.7.2.2 Missing or Incomplete Data and Lost to Follow-up

We are describing pregnancy and infant outcomes among women exposed to Repatha during pregnancy. We are not assessing associations, so missing or incomplete data will not cause bias. However, it may affect the accuracy of our reporting on the description of the population and outcomes. Due to self-report, women with adverse events may be more likely to report than women without. This may result in overestimation of the proportion of exposed pregnancies with adverse outcomes.

8.7.2.3 Descriptive Analysis

8.7.2.3.1 Description of Study Enrollment

Descriptive results will be presented in each annual interim report.

8.7.2.3.2 Description of Patient Characteristics

Patients will be pregnant women exposed to Repatha during pregnancy. Demographic characteristics of subjects will be summarized using descriptive statistics. Continuous

variables will be summarized using the mean, standard deviation, median, and range. Categorical variables will be summarized using frequencies and counts.

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

All analyses will be descriptive. These cases constitute a case series, thus line listings of pregnancy and maternal complications, pregnancy outcomes, infant outcomes and adverse events will be summarized along with tabulations of the numbers and frequencies of events by category of report: numbers who did not provide consent for follow-up, timing of exposure (first, second, or third trimester), and indication for use of the medication. Collection of exposure and outcome information in this group provides additional evidence on the safety of Repatha use during pregnancy. The denominator is the number of pregnant women exposed to Repatha during pregnancy and the numerator is the number with the outcome.

The proportion of infants with adverse events including complications, medical problems or congenital anomalies at birth will be assessed in infants of women exposed to Repatha during pregnancy with corresponding 95% confidence intervals. The proportion of infants with adverse events at 6 months and 12 months of age will be assessed. All adverse events among mothers who have received Repatha at any time during the pregnancy will be summarized including the proportion with pregnancy and maternal complications. To assess events in the developing fetus and neonate in women exposed to Repatha during pregnancy, the proportion of pregnancies resulting in spontaneous abortions, elective abortions, fetal death/ stillbirths and premature delivery will be presented, along with corresponding 95% confidence.

If the available safety information relevant to exposure during pregnancy represents a safety signal, the signal will be further evaluated through the Amgen safety governance structure and, if deemed necessary, escalated for consideration of changes to the Reference Safety Information (eg, USPI) as well as other forms of risk communication (eg, Dear Healthcare Provider Letters).

8.7.2.4 Sensitivity Analysis

Not applicable.

8.7.2.4.1 Subgroup Analysis

Not applicable.

8.7.2.4.2 Stratified Analysis

Not applicable.

8.7.2.4.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

8.7.2.4.4 Other Sensitivity Analysis

Not applicable.

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

This study includes secondary postmarket data of pregnant women exposed to Repatha and their infants through the first year of life. All outcomes in this study are safety endpoints including pregnancy and maternal complications, pregnancy outcomes, infant outcomes and adverse events reported through the Amgen Global Safety Database.

8.7.4 Quality Control

See Section 8.6.

8.7.5 Limitations of the Research Methods

8.7.5.1 Internal Validity of Study Design

8.7.5.1.1 Measurement Error(s)/Misclassification(s)

Identification of pregnant women exposed to Repatha depends upon the accuracy of the incoming information received by Amgen's Global Safety Database. Amgen has a comprehensive system to detect these events and a process to verify the data. However, the postmarket data may have missing information which could lead to not classifying the report as a pregnancy case.

Misclassification of outcomes due to poor patient recall should be reduced in this retrospective and prospective study design. For those women exposed to Repatha during pregnancy that are identified retrospectively, they are likely to accurately recall any maternal complications, pregnancy outcomes, adverse infant outcomes and events that may have occurred. However, exposed pregnant women that do not experience complications or adverse events may be less likely to consent to follow-up or may be lost to follow-up which would affect the denominators for aggregate outcomes.

A limitation of the study design relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion, ie, at 7 to 9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. The study results with respect to spontaneous abortion will be limited to cases of late first-trimester and early second-trimester pregnancy loss.

Also, the calculation of frequency of birth defects excludes fetal losses (spontaneous abortions, elective abortions, or fetal deaths) for which no birth defects have been

detected. This may introduce a misclassification bias as there is no uniform evaluation of embryos or fetuses that do not survive. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or structural defects. Amgen Global Safety will attempt to obtain information on structural defects detected at the time of the outcome. However, the malformation status of the aborted fetus may not be known. Therefore, defects reported in these groups will be considered separately from the primary analysis.

8.7.5.1.2 Information Bias

Not applicable.

8.7.5.1.3 Selection Bias

Pregnant women exposed to Repatha during pregnancy who consent to share their information with Amgen may be different from those who do not and may affect the accuracy of our estimates as discussed in section 8.7.2.2.

8.7.5.1.4 Confounding

Since this is a descriptive study and there is no comparison group, confounding will not be measured in the study.

8.7.5.2 External Validity of Study Design

The findings of this study will be generalizable to any pregnant woman exposed to Repatha.

8.7.6 Analysis Limitations

None. The study is descriptive.

8.7.7 Limitations Due to Missing Data and/or Incomplete Data

Some patients may be lost to follow-up resulting in missing data. Patients that are lost to follow-up may differ from those that remain in the study and this could be an issue in this study.

8.8 Other Aspects

None.

9. Protection of Human Subjects

This study will be conducted in compliance with the protocol and protections in place during the collection of safety data through the AGS system, International Society for Pharmacoepidemiology's Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the US, US FDA regulatory requirements, in accordance with the ethical principles of the Declaration of Helsinki (1995), and the Health Insurance

Portability and Accountability Act (HIPAA) (US Department of Health and Human Services, 2003; US Department of Health and Human Services, 2002; International Society for Pharmacoepidemiology, 1996).

9.1 Informed Consent

Informed consent is required to perform follow-up for pregnancy, birth and health information of the mother and infant.

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

There is not an IRB/IEC for this study.

9.3 Subject Confidentiality

No personal identifiers will be included in the data analyses or reporting from the Amgen Global Safety Database for this study.

9.4 Subjects Decision to Withdraw

All exposed women are identified from postmarketing reports to the Amgen Global Safety Database. Consent for follow-up is the responsibility of Amgen Global Safety. Subjects are free to withdraw consent at any time.

10. Collection, Recording, and Reporting of Safety Information and Product Complaints

This is a retrospective and prospective observational case series analyzing pre-existing data within the Amgen Global Safety Database for women exposed to Repatha during pregnancy. Collection, recording and reporting of safety information and product complaints is not applicable because for this study because all data reported for the study has been previously received in the Amgen Global Safety Database and reported as required in accordance with local requirements to regulatory authorities, or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations.

11. Administrative and Legal Obligations

11.1 Protocol Amendments and Study Termination

If Amgen plans to amend the protocol, a proposed protocol amendment will be sent to the FDA for review and agreement before initiating any changes to the study conduct.

Amgen will not terminate the study unless agreement to do so has been given by the FDA.

12. Plans for Disseminating and Communicating Study Results

The findings from this study will be included in annual interim reports submitted to the FDA in September 2022, 2023, 2024, 2025 and the final report in 2026.

12.1 Publication Policy

These analyses will not be submitted for publication.

13. References

Amgen, Inc. Prescribing Information for Evolocumab. Thousand Oaks, CA: Amgen, Inc. July 2016.

Bartels A, Egan N, Broadhurst DI, et al. Maternal serum cholesterol levels are elevated from the 1st trimester of pregnancy: a cross-sectional study. J Obstet Gynaecol. 2012;32(8):747-752.

Brown MS, Goldstein JL. Biomedicine. Lowering LDL--not only how low, but how long? Science. 2006;311(5768):1721-1723.

Connor WE, Cerqueira MT, Connor RW, Wallace RB, Malinow MR, Casdorph HR. The plasma lipids, lipoproteins, and diet of the Tarahumara indians of Mexico. Am J Clin Nutr. 1978;31(7):1131-1142.

DeSesso JM, Williams AL, Ahuja A, Bowman CJ, Hurtt ME. The placenta, transfer of immunoglobulins, and safety assessment of biopharmaceuticals in pregnancy. Crit Rev Toxicol. 2012;42(3):185-210.

Dietschy JM, Turley SD, Spady DK. Role of liver in the maintenance of cholesterol and low density lipoprotein homeostasis in different animal species, including humans. J Lipid Res. 1993;34(10):1637-1659.

Homanics GE, Smith TJ, Zhang SH, Lee D, Young SG, Maeda N. Targeted modification of the apolipoprotein B gene results in hypobetalipoproteinemia and developmental abnormalities in mice. Proc Natl Acad Sci U S A. 1993;90(6):2389-2393.

Horton JD, Cohen JC, Hobbs HH. Molecular biology of PCSK9: its role in LDL metabolism. Trends Biochem Sci. 2007;32(2):71-77.

International Conference on Harmonisation (ICH). Tripartite Guideline M3 (R2) Guidance on nonclinical safety studies for the conduct of human clinical trials and marketing authorization for pharmaceuticals. 2009.

McMurry MP, Connor WE, Goplerud CP. The effects of dietary cholesterol upon the hypercholesterolemia of pregnancy. Metabolism. 1981;30(9):869-879.

Seidah NG, Benjannet S, Wickham L, et al. The secretory proprotein convertase neural apoptosis-regulated convertase 1 (NARC-1): liver regeneration and neuronal differentiation. Proc Natl Acad Sci U S A. 2003;100(3):928-933.

Woollett LA. Maternal cholesterol in fetal development: transport of cholesterol from the maternal to the fetal circulation. Am J Clin Nutr. 2005;82(6):1155-1161.

14. Appendices

Appendix A. List of Stand-alone Documents

None.

Appendix B. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

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

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

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

Study Title: An observational case series to describe women exposed to Repatha during pregnancy including pregnancy and infant outcomes during the first year of life

EU PAS Register® number:
Study reference number (if applicable): 20200408

Section 1: Milestones		**Yes**	**No**	**N/A**	**Section Number**
1.1	Does the protocol specify timelines for				
	1.1.1 Start of data collection[1]	☒	☐	☐	8.2.1
	1.1.2 End of data collection[2]	☒	☐	☐	8.2.1
	1.1.3 Progress report(s)	☐	☒	☐	
	1.1.4 Interim report(s)	☒	☐	☐	8.7.1.1
	1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
	1.1.6 Final report of study results.	☒	☐	☐	8.2.1

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

Comments:

Need to add EU PAS Register information.

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
	2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	6.2
	2.1.2 The objective(s) of the study?	☒	☐	☐	7.1
	2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	8.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	6.3
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

No hypotheses will be tested in the study.

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	8.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	8.2
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	8.3.2
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☐	☒	☐	
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	8.3.2

Comments:

There is no comparison group so no measures of association.

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	8.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	8.2.1
4.2.2 Age and sex	☒	☐	☐	8.2
4.2.3 Country of origin	☒	☐	☐	8.2
4.2.4 Disease/indication	☒	☐	☐	8.2.1
4.2.5 Duration of follow-up	☒	☐	☐	8.2.5
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	8.2.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	8.3.1
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	8.3.1
5.3 Is exposure categorised according to time windows?	☒	☐	☐	8.3.1
5.4 Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	8.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	8.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

This is a single arm study with no comparators.

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	8.3.2
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	8.3.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

These outcomes are not relevant for this study.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☐	☒	8.7.5.1.4
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☐	☐	☒	8.7.5.1.3
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	8.7.5.1.2

Comments:

There is no comparison group so measurement of bias and confounding is not applicable to this study.

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

Comments:

Effect measure modification is not applicable to this study.

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	8.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	8.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	8.4
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	8.3.1
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.3.2
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	8.3.2
9.3.3 Covariates and other characteristics?	☐	☒	☐	8.3.3
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Exposure coding is not applicable because all women in the study are exposed to Repatha. Outcomes, covariates and other characteristics are based on report from the mother or HCP and will be reported descriptively. No linkage will be performed.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	8.7.2.1
10.2 Is study size and/or statistical precision estimated?	☐	☒	☐	8.5
10.3 Are descriptive analyses included?	☒	☐	☐	8.6.2.4
10.4 Are stratified analyses included?	☐	☐	☒	8.7.2.4.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	8.7.5.1.1
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	8.7.2.2
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

There is no comparison group so confounding will not be measured. Due to the descriptive nature of the study, no sensitivity analyses will be conducted.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	8.6
11.2 Are methods of quality assurance described?	☒	☐	☐	8.6
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

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

Comments:

This is a single arm study so bias and confounding will not impact the results. This is a case series so study feasibility is not applicable.

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☐	☐	☒	
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	9.3

Comments:

Cases for this study are drawn from the Amgen Global Safety Database.

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	11.1

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12.1

Comments:

Name of the main author of the protocol: PPD

Date: 13 /October/2020

Signature: _____

Appendix C. Initial Pregnancy Questionnaire – Mother

AMGEN

Safety Database # _____

INITIAL PREGNANCY QUESTIONNAIRE (MOTHER)

You may return completed form to Amgen Office Fax or Email:

Fax: (888) 814-8653 Email: svc-ags-in-us@amgen.com

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other _____ Parent exposed to product? ☐ Mother ☐ Father

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

*Did the patient sign the Authorization for Release of Medical Information? ☐ Yes ☐ No

In the event your contact information changes, please provide a back-up contact (for example a close relative or friend who does not live with you) who we may reach in an effort to contact you.

Relationship to patient: _____

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

Section 2 – Mother Current Pregnancy Information

Mother's Initials: _____

Age: _____years

Number of fetuses: _____

Date of birth: (if permitted to provide by local laws) _____ Day Month Year

Date of last menstrual period: _____ Day Month Year

Estimated date of delivery: _____ Day Month Year

Relevant Laboratory Tests & Procedures

Test Name	Test Date (dd/mm/yr)	Test Result

Section 3 – Mother Prenatal Medication History

Please list all medications (prescription and over-the-counter [include vitamins, herbal medications, etc.) and vaccines, taken by the **mother within 3 months prior to or during pregnancy**.

Amgen Product Used	Dose	Route (e.g. oral, subcutan.)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Weeks of Pregnancy When Drug Taken (e.g. wk 28–wk 32)	Indication for Treatment
Resumed (if applicable)							
Amgen Product Lot Number _____ ☐ Lot Number Not Known							

AMGEN **Safety Database #** _____

List any other medications used within 3 months prior to or during the pregnancy

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 4 – Pregnancy Complication and Adverse Event Information

If the **mother** experienced any pregnancy complications (e.g. preeclampsia, gestational diabetes, placenta previa, etc.) please complete the following:

Pregnancy Complication or Adverse Event	Date the Complication or Event Started (dd/mm/yy)	Date the Complication or Event Resolved (dd/mm/yr)	Outcome (for example: resolved, not resolved, unknown, other, etc.)

Section 5 – Mother Relevant Medical History

Please provide pertinent medical history:

☐ hypertension ☐ seizure ☐ diabetes ☐ difficulty conceiving ☐ asthma ☐ thyroid dysfunction ☐ other _____

Please describe any additional factors that may have an impact on the outcome of this pregnancy, including relevant medical or family history, mother's occupation, illnesses during pregnancy etc. Please specify other disorders including familial birth defects/genetic/chromosomal disorders, etc.:

Section 6 – Mother Previous Obstetrical (Pregnancy) History

Please provide the number of pregnancies after treatment with an Amgen product was initiated and the pregnancy outcome for each of these pregnancies and any additional relevant details:

Number of pregnancies and outcome details:

☐ Normal healthy baby: _____ ☐ Miscarriage: _____

☐ Stillbirth: _____ ☐ Abortion (induced for medical reason): _____

☐ Baby with birth defect: _____ _____

☐ Outcome unknown: _____ _____

AMGEN **Safety Database #** _____

☐ Abortion (induced for non-medical [voluntary] reason): _____

_____

☐ Other (specify outcome) or any significant additional information:

Section 7 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (please check the appropriate box below):

☐ Live birth
- ☐ Number of infants_____(1: single, 2: twins, etc.) (If multiple births: Please provide all information for each infant in the additional information text box below:)

If live birth: Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight _____gram/lb

Head circumference: _____cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)?

☐ Yes

☐ No

If yes, please provide specific information below.

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
- ☐ Due to health issue (mother or baby)
- ☐ For voluntary reason
- ☐ Other (please specify): _____

_____

Please confirm if there were there any tests done or results given for the baby/fetus? ☐Yes ☐No
If yes, please provide the details below.

Additional Information on pregnancy outcome:

AMGEN® **Safety Database #** _____

Section 8 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____

Health Care Provider for the child:

Name _____ Phone ( ) _____ Fax ( ) _____

Email _____ Address _____ City _____

State/Province _____ Zip/Postal Code _____ Country _____

Appendix D. 6 to 8 Weeks Post Due Date Questionnaire – Mother

Safety Database # [case_id]

You may return completed form to Amgen Office Fax or Email:

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER)

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Health Care Professional ☐ Other _____

Any change in the reporter contact information? ☐ Yes ☐ No If yes, please provide updated contact information:

Name _____Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 2 – Mother Prenatal Medication History

Please provide any additional medication information for medicines used during your pregnancy not previously reported. For example, if you resumed or discontinued the Amgen Product or any other medications during the pregnancy (include vitamins, folic acid, herbal medications, and vaccines).

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly)	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Section 3 – Mother Pregnancy Complications and/or Adverse Event Information

Pregnancy Complication or Adverse Event (e.g. preeclampsia, gestation diabetes)	Date the Complication or Event Started (dd/mm/yy)	Date the Complication or Event Resolved (dd/mm/yr)	Outcome (for example: resolved, not resolved, unknown, other, etc.)

Amgen Proprietary - For Internal Use Only

AMGEN Safety Database # [case_id]

6 TO 8 WEEKS POST DUE DATE QUESTIONNAIRE (MOTHER) *continued*

Section 4 – Mother Current Pregnancy Outcome (if applicable)

Date pregnancy ended: _____
Day Month Year

Weeks of pregnancy at delivery (or if the outcome was a loss of pregnancy): _____ weeks

Pregnancy Outcome (please check the appropriate box below)

☐ Live birth
  ☐ Number of infants_____(1: single, 2: twins, etc.)
  (If multiple births: Please provide all information for each infant in the additional information text box below:)

☐ Pregnancy loss (miscarriage)
☐ Stillbirth
☐ Termination
  ☐ Due to health issue (mother or baby)
  ☐ For voluntary reason
  ☐ Other (please specify):_____

If live birth: Gender: ☐ Male ☐ Female

Length: _____cm/inches Birth weight: _____gram/lb Head circumference: _____ cm/inches

Did the baby have any complications/medical problems/congenital anomalies (birth defects)? ☐ Yes ☐ No
If yes, please provide specific information below.

Additional Information on pregnancy outcome:

Section 5 – Reporter Signature

Signature of person completing questionnaire: _____ Date: _____

Please print name: _____

Title and specialty if HCP: _____

For consumers/patients only. Please provide contact information for your and your child's HCPs
May Amgen contact your HCP? ☐ Yes ☐ No

Health Care Provider for the pregnancy/delivery:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider who is prescribing the Amgen product:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____

Health Care Provider for the child:

Name _____Phone ( ) _____Fax ( ) _____

Email _____Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Appendix E. 6- and 12-month Infant Questionnaire

Mother Safety Database #	
Infant Safety Database #	

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

From: {Title} {First Name} {Last Name} {Company Name} {Country}	[today]
To:[reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact]	

Event: Pregnancy	**Product**: [product_name]:[1]
AER#: [case_id]	**Reply Due By**: {Due Date}

Dear [reporter_first_name:corresp_contact] [reporter_last_name:corresp_contact],

Thank you for reporting your [patient_initials] pregnancy while on [product_name:first_suspect] ([generic_name:first_suspect]) therapy. Please send the completed questionnaire with requested information to the address, email or fax below.

Kindly note the following attachments:

- **SIX AND TWELVE MONTH INFANT QUESTIONNAIRE**

Respectfully Yours,

{Title} {First Name} {Last Name}
{Company Name} {Country}
Email: {email}
Fax: {fax}
Phone: {phone}

Mother Safety Database #

Infant Safety Database #

AMGEN

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

You may return completed form to Amgen Office Fax or Email:

Section 1 – Reporter Information

Reporter: ☐ Mother ☐ Father ☐ Health Care Professional (HCP) ☐ Other_____

Section 2 – Infant Healthcare Provider (HCP) Information

May Amgen contact the HCP for medical information regarding your child? ☐ Yes ☐ No

If yes, please provide contact information:

Name _____ Phone ( ) _____Fax ( ) _____

Email _____ Address _____City _____

State/Province _____Zip/Postal Code _____Country _____

Section 3 – Infant Medical Health Information

List any other medications/drugs (include vitamins and over-the-counter medications taken by the child)

Medications/Drugs	Dose	Route (e.g. oral, subcutaneous)	Frequency (e.g. daily, weekly	Date Drug Started (dd/mm/yy)	Date Drug Stopped (dd/mm/yy)	Indication for Treatment

Has the infant had any abnormal screening tests? ☐ Yes ☐ No If yes, please explain:

Has the infant followed growth curves and developmental milestones as expected for chronological age?

☐ Yes ☐ No If no, please explain:

Has the infant had any illnesses or persistent health problems? ☐ Yes ☐ No If yes, please explain:

Section 4 – Reporter Signature

Signature of person completing questionnaire: _____Date: _____

Please print name: _____Title and specialty if HCP_____

Approval Signatures

Document Name: Protocol-Published Original Evolocumab 20200408

Document Description:

Document Number: CLIN-000272100

Approval Date: 16 Jul 2021

Type of Study Protocol: Original

Protocol Amendment No.:

Document Approvals	
Reason for Signing: Functional Area	Name: Siddique Abbasi Date of Signature: 16-Jul-2021 16:11:07 GMT+0000