PASS INFORMATION

Title	An Observational Case Series to Describe Women Exposed to Repatha During Pregnancy and Infant Outcomes During the First Year of Life
Version Identifier of the Final Study Report	Study 20200408, Interim Analysis Report 4, Version 1.0
Date of Last Version of the Study Report	30 August 2024
EU PAS Register No:	EUPAS42393
Active Substance	evolocumab (Anatomical Therapeutical Code [ATC]: C10AX13)
Medicinal Product	Repatha®
Product Reference:	Not Applicable
Procedure Number:	Not Applicable
Marketing Authorization Holder	Amgen Inc.
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 of Study	Global

Authors	PPD , Senior Manager, Observational Research Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD PPD Senior 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, Observational Research, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD PPD Medical Director, Global Safety, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD PPD Senior Manager, Global Safety, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD PPD Senior Manager, Global Safety, Amgen Inc., One Amgen Center Drive,

	Thousand Oaks, CA 91320 PPD

Marketing Authorization Holder

Marketing Authorization Holder	Amgen Inc.
MAH Contact Person	PPD Regulatory Affairs Manager, Amgen Inc., One Amgen Center Drive, Thousand Oaks, CA 91320 PPD

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1. ABSTRACT

- **Title**

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

Date of Abstract: 09 September 2025

Authors:
PPD Senior Manager, Observational Research, Amgen Inc.;
PPD Senior Manager, Observational Research, Amgen Inc.;
PPD Director Observational Research, Amgen Inc.;
PPD Director Observational Research, Amgen Inc.;
PPD Medical Director, Global Safety, Amgen Inc.;
PPD Senior Manager, Global Safety, Amgen Inc.
PPD Senior Manager, Global Safety, Amgen Inc.

- **Keywords**

pregnancy, postmarketing, malformations, hypercholesterolemia

- **Rationale and Background**

This study is being conducted to address a Food and Drug Administration (FDA) postmarketing requirement to conduct an observational study of pregnant women exposed to Repatha® (evolocumab) to evaluate maternal complications and fetal and infant outcomes through the first year of life. This study estimates the proportion of pregnancy and maternal complications, adverse events for the developing fetus and neonate, and adverse events for the infant through the first year of life using data from individual case reports within Amgen's Global Safety Database.

This fourth interim report provides the analysis of the data collected from the first marketing approval date of 17 July 2015 through the data cutoff date of 17 July 2025.

- **Research Question and Objectives**

Primary Objective: 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.

- **Study Design**

This is a worldwide, single-arm, observational case series that analyzes prospective and retrospective data in women exposed to Repatha during pregnancy, collected routinely within the Amgen's Global Safety Database.

Data were extracted from individual case reports obtained from Amgen's Global Safety Database for women exposed to Repatha during pregnancy and their infants between 17 July 2015 and the approval date of the protocol (Version 1.0, 14 April 2021) and prospectively, from approval date of the protocol through the current data cutoff date of 17 July 2025. All case reports were analyzed for women who had been exposed to Repatha during their pregnancy and among their infants.

- **Setting**

The study population included women worldwide, exposed to Repatha® during pregnancy that consented for pregnancy and infant follow-up.

- **Participants and Study Size, Including Dropouts**

Women exposed to Repatha® during pregnancy or within up to 90 days before their last menstrual period (LMP) and their infants through the first year of life who consented to provide their information to Amgen were included in the study. The study size was dependent on the number of reports submitted to the Amgen's Global Safety Database for women exposed to Repatha during pregnancy. Pregnancies involving paternal Repatha exposure and infants with Repatha exposure through lactation were not included.

- **Data Sources and Methods**

Amgen's 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 postmarket sources. Amgen performs follow-up on adverse events reported for all products including Repatha as per Amgen's due diligence process. The database includes reports of pregnancy, birth outcome, and infant health information of women who had direct exposure to Repatha before 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 could include multiple pregnancies from the same woman), of which Amgen became 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 noninterventional studies) and reported from clinical trials were entered into the Amgen's Global Safety Database. Pregnancy exposure case reporting and follow-up through the infant's first year of life were voluntary and patients were free to withdraw their consent at any time. For the purposes of this study, all Repatha pregnancy cases were retrieved from the Amgen's Global Safety Database.

Amgen did not provide compensation for participation in the follow-up process.

As per Amgen's due diligence process, upon notification of Repatha exposure during pregnancy (with or without an adverse event), Amgen Global Patient Safety followed-up with the reporter to request informed consent to obtain pregnancy and infant health information from the mother. Follow-up was performed as per Amgen's routine pharmacovigilance process at predefined intervals and adjusted accordingly depending on whether the mother was pregnant or had already delivered. Information requested included, but was not limited to, pregnancy/delivery details, medical history, laboratory and diagnostic tests, and healthcare provider names. The process included a set number of follow-up attempts over predefined intervals (post birth, when the infant was 6 months and 12 months). If there was no response to the follow-up attempts, the due diligence process was considered complete, and the case was considered lost to follow-up. An exception to this process occurred when the reporter explicitly stated they were 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 occurred, follow-up was not conducted. Amgen makes a concerted effort to obtain follow-up information. A high-level overview of the Amgen follow-up process for pregnancy reports including flow charts are provided in Appendix 4.

- **Variables**

Outcome Variables:

The outcomes for the study included the occurrence and dates of pregnancy and maternal complications, pregnancy outcomes, and infant outcomes based on self-report. Pregnancy outcomes included the number of cases that reported live full-term births, spontaneous abortion, elective abortion, fetal death/stillbirth, and premature delivery. Infant outcomes were the number of cases that reported adverse events, including complications, medical problems, or congenital anomalies at birth, as well as the number of cases that reported adverse events at 6 months and 12 months. These events may have included failure to follow growth curves or failure to meet developmental milestones expected for chronological age.

Exposure Variables:

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

Other Covariates:

Other covariates were included that pertained to maternal information, exposure, and pregnancy and delivery. Maternal covariates included demographic information for the mother, pregnancy history, medical history, and other relevant history that may have impacted the pregnancy (e.g., family history, mother's occupation). Variables related to exposure included current medications and dates of use (prescription and over-the-counter [OTC]), and the occurrence and dates of current pregnancy complications. Characteristics of pregnancy and delivery, such as maternal conditions, birth information, delivery details, and newborn complications, were also recorded.

- **Results**

For this fourth annual report, cumulatively 187 pregnancies with reported Repatha exposure were retrieved using the search criteria from 17 July 2015 through the data cutoff date of 17 July 2025. In comparison to the third interim analysis report, there were 26 new pregnancies exposed to Repatha from 17 July 2024 through 17 July 2025 that met this study's inclusion criteria. Among the 187 pregnancies, the median (Q1, Q3) age of mothers at pregnancy was 34.0 (30.0, 38.0) years. Relevant medical history included diabetes (4 cases, 2.1%), thyroid dysfunction (3 cases, 1.6%), difficulty conceiving (2 cases, 1.1%), hypertension (2 cases, 1.1%), asthma (1 case, 0.5%), and other medical history conditions (29 cases, 15.5%) which were largely cardiovascular and gastrointestinal related disorders. Reported maternal or pregnancy complications included gestational diabetes (5 cases), pre-eclampsia/ eclampsia (1 case), and other complications (7 cases) included cardiovascular complications, gestational hypertension, and superficial wound infection from cesarean section.

As of the data cutoff date, among all pregnancies (n = 187), pregnancy outcomes were known for 57 (30.5%) pregnancies and unknown or lost to follow-up for 130 (69.5%) pregnancies. Overall, live birth was reported for 36 pregnancies, including 1 case of a twin birth; of which 7 pregnancies were full-term, 1 was pre-term birth, 1 was post-term birth, and the gestational timing could not be determined for the remaining 27 live births as the date of LMP was unknown. Birth weight was known in 11 pregnancies, with the median (Q1, Q3) birth weight being 3400.0 (2840.0, 3945.0) grams.

Spontaneous abortion was reported for 14 pregnancies, fetal death/stillbirth for 5 pregnancies, and elective abortion for 2 pregnancies.

In this interim analysis report 4, one pregnancy that was reported as an elective abortion in the interim report 3 has been reclassified as a spontaneous abortion following clinical review. The case involved a fetal death at the end of the ninth week of gestation, which did not meet the definition of elective termination and was therefore determined to be more accurately categorized as a spontaneous abortion. In total, 2 pregnancies resulted in elective abortion and 5 pregnancies resulted in fetal death/stillbirth as of the data cutoff date (17 July 2025).

No congenital anomalies were reported. Out of 36 infants for which information was available, there were no reports of abnormal growth curves, delayed developmental milestones, premature delivery, abnormal screening tests, or persistent health problems.

- **Discussion**

Women exposed to Repatha during pregnancy or within up to 90 days before their LMP identified for this report were all indicated to receive Repatha, and thus this patient population had known baseline cardiovascular medical conditions and can be largely predisposed to health risks. Among the 5 pregnancies which resulted in fetal deaths, all women had at least 1 of the following medical history: familial hypercholesterolemia, aortic valve replacement, family history of early onset coronary artery disease, and hypertensive disorders. Of the 14 cases of spontaneous abortion, 13 women had at least 1 of the medical history, which included familial hypercholesterolemia, coronary artery bypass graft (CABG), hypothyroidism, aortic stenosis, cardiovascular events, advanced maternal age, ovarial cyst, high cholesterol, or dyslipidemia; and 1 woman had no reported medical history. It is important to note that the outcome remains unknown for a major proportion of these pregnancies—130 cases (69.5%). Consequently, any estimates derived from the reported outcomes should be interpreted considering this limitation.

Based on available data as of the data cutoff date of 17 July 2025, there are no safety concerns identified. Interpretation of data is limited by a high rate of missing outcome data. However, these conclusions remain preliminary till final study report submission in September 2026. The overall observed rate of adverse pregnancy outcomes such as spontaneous abortion and fetal death, among women exposed to Repatha during pregnancy or within 90 days prior to their LMP and among their infants during the first year of life is low. Amgen will continue to monitor Repatha safety in pregnant women.

- **Marketing Authorization Holder**

Amgen Inc.

- **Names and Affiliations of Principal Investigators**

Not applicable.

2. LIST OF ABBREVIATIONS

Abbreviation or Term	Definition/Explanation
CI	Confidence interval
FDA	Food and Drug Administration
HCP	Health care provider
LDL	low-density lipoprotein
LDL-C	low-density lipoprotein cholesterol
LMP	last menstrual period
PBRER	Periodic Benefit-Risk Evaluation Report
PCSK9	proprotein convertase subtilisin kexin type 9
US	United States

3. INVESTIGATORS

Not applicable.

4. OTHER RESPONSIBLE PARTIES

A panel of 3 independent contractors with expertise in teratology, pediatrics, and dysmorphology have been contracted to be external adjudicators for any medical records of major malformations found in maternally exposed infants. However, no congenital malformations have been reported to date.

5. MILESTONES

The milestones for this study are provided in Table 5-1.

Table 5-1. Study 20200408 Milestones

Milestone	Planned Date	Actual Date	Comments
Start of data collection	17 July 2022	17 July 2022	
End of data collection	July 2025	-	
Registration in the EU PASS register	24 August 2021	24 August 2021	
Interim report 1	September 2022	06 September 2022	
Interim report 2	September 2023	15 September 2023	
Interim report 3	September 2024	30 August 2024	
Interim report 4	September 2025	09 September 2025	
Final report of study results	September 2026	-	

EU PASS = European Union Post-authorization Safety Studies

6. RATIONALE AND BACKGROUND

In the United States (US), Repatha is a PCSK9 (proprotein convertase subtilisin kexin type 9) inhibitor indicated:

- To reduce the risk of major adverse cardiovascular (CV) events (CV death, myocardial infarction, stroke, unstable angina requiring hospitalization, or coronary revascularization) in adults at increased risk for these events.
- As an adjunct to diet and exercise to reduce low-density lipoprotein cholesterol (LDL-C) in:
    - adults with hypercholesterolemia.
    - adults and pediatric patients aged 10 years and older with heterozygous familial hypercholesterolemia (HeFH).
    - adults and pediatric patients aged 10 years and older with homozygous familial hypercholesterolemia (HoFH).

Currently, available data from clinical trials and postmarketing reports on Repatha use in pregnant women are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes (Section 8.1 of Repatha Prescribing Information).

In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were subcutaneously administered Repatha from organogenesis through parturition at dose exposures up to 12 times the exposure at the maximum recommended human dose of 420 mg every month. 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. Measurable Repatha serum concentrations were observed in the infant monkeys at birth at comparable levels to maternal serum, indicating that Repatha, like other immunoglobulin G antibodies, crosses the placental barrier. Monoclonal antibodies are transported across the placenta in increasing amounts especially near term; therefore, Repatha has the potential to be transmitted from the mother to the developing fetus (Section 8.1 of Repatha Prescribing Information).

The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively (Section 8.1 of Repatha Prescribing Information).

6.1 Diseases and Therapeutic Area

A serine protease expressed predominantly in the liver, kidney, and intestine (Seidah et al, 2003), PCSK9, plays an important role in the recycling and regulation of the low-density lipoprotein (LDL) receptor (Horton et al, 2007; Brown and Goldstein, 2006). The PCSK9 acts through direct binding to the LDL receptor, resulting in posttranslational 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 immunoglobulin G2 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; International Council for Harmonisation, 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 anticipated to be 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).

6.2 Rationale

This study is being conducted to address a Food and Drug Administration (FDA) postmarketing requirement to conduct a prospective and retrospective observational study of pregnant women exposed to Repatha in the Amgen's Global Safety Database,

to evaluate maternal complications and fetal and infant outcomes through the first year of life.

7. RESEARCH QUESTION AND OBJECTIVES

The primary objective is, 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.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

A summary of the study design is provided below. Full details of the study design are provided in the study protocol (Annex 2).

9.1 Study Design

This is a worldwide, single-arm, observational case series that analyzes prospective and retrospective data in women exposed to Repatha during pregnancy, collected routinely within the Amgen's Global Safety Database.

Data were extracted from individual case reports obtained from Amgen's Global Safety Database for women exposed to Repatha during pregnancy and their infants between 17 July 2015 and the approval date of the approved protocol (Version 1.0, 14 April 2021) and prospectively, from the approval date of the protocol through the current data cutoff date of 17 July 2025. All case reports were analyzed for women who had been exposed to Repatha during their pregnancy and among their infants.

9.2 Setting

The study population included women, worldwide, exposed to Repatha during pregnancy that consented for pregnancy and infant follow-up. Case information was obtained through the Amgen's Global Safety Database which included: clinical trial, spontaneous reporting (including regulatory authority and literature), solicited (ie, patient support programs and market research), and postmarketing noninterventional studies.

9.3 Participants

Women exposed to Repatha during pregnancy or within up to 90 days before their LMP and their infants through the first year of life who consented to provide their information to Amgen were included in the study. The study size was dependent on the number of reports submitted to the Amgen's Global Safety Database for women exposed to Repatha during pregnancy. Pregnancies with paternal Repatha exposure and infants with Repatha exposure through lactation were not included.

For the purposes of this study, all Repatha pregnancy cases were retrieved from the Amgen's Global Safety Database and included in this analysis.

9.4 Variables

9.4.1 Exposure Assessment

The period defining exposure to Repatha during pregnancy was any number of days, at any dose, and at any time from 90 days before the first day of the LMP up to and

including the end of pregnancy. Identification of pregnancy was through the Amgen's Global Safety Database search.

9.4.2 Outcome Assessment

Outcomes included the number of women reporting for the following:

- Pregnancy or maternal complications
- Live full-term births
- Spontaneous abortion, defined as nondeliberate fetal death, which occurs up to 20 completed weeks post-LMP
- Elective abortion, defined as deliberate termination of pregnancy before 20 weeks of gestation
- Fetal death/stillbirth defined as nondeliberate fetal death after 20 completed weeks and stillbirth after 28 completed weeks post-LMP, and
- Premature delivery is defined as live birth before 37 weeks of gestation as counted from LMP (eg, ultrasound adjusted date or Ballard's score).

Outcomes related to pregnancy and maternal complications were assessed with a Pregnancy Questionnaire (a sample form included in Protocol Appendix C [Annex 2 of this report]). Outcomes for live births were assessed with a Post Due Date Questionnaire (a sample form included in Protocol Appendix D [Annex 2 of this report]) from the Amgen's Global Safety Database.

The number of infants with adverse events including complications, medical problems or congenital anomalies at birth were assessed with a Post Due Date Questionnaire (a sample form included in Protocol Appendix D [Annex 2 of this report]) from the Amgen's Global Safety Database.

Major malformations or birth defects were 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 amongst infants up to 1 year of age by the mother or the healthcare provider (HCP) were included in the primary analysis. Major structural birth defects could have been reported by the mother, a family member, or her or her child's HCP through medical records. If a major malformation was reported, the medical record was adjudicated by a physician with expertise in teratology, pediatrics,

and dysmorphology. Defects were classified using the Center for Disease Controls criteria (Centers for Disease Control and Prevention, 2023).

Infant outcomes were the number of cases reporting adverse events at 6 months and 12 months after birth and included whether they had not followed growth curves or met development milestones as expected for chronological age. These outcomes were assessed with an Infant Questionnaire (a sample form included in Protocol Appendix E [Annex 2 of this report]).

Post due date variables related to pregnancy and delivery such as maternal conditions, newborn complications, birth information, and delivery details were reported.

9.4.3 Covariate Assessment

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

9.4.4 Validity and Reliability

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

9.5 Data Sources and Measurement

The Amgen's 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 postmarket sources. Amgen performs follow-up on adverse events reported for all products including Repatha as per Amgen's due diligence process. The Amgen's Global Safety Database includes reports of pregnancy, birth outcome, and infant health information of women who had direct exposure to Repatha before 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 could include multiple pregnancies from the same woman), of which Amgen became 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 noninterventional studies) and from clinical trials were entered into the Amgen's Global Safety Database. Pregnancy exposure case reporting and follow-up through the infant's first year of life were voluntary and patients were free to withdraw their consent at any time.

Amgen did not provide compensation for participation in the follow-up process.

As per Amgen's due diligence process, upon notification of 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 is 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 includes, 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 included a set number of follow-up attempts over predefined intervals (post birth, when the infant was 6 months and 12 months). If there was no response to the follow-up attempts the due diligence process was considered complete and the case was considered lost to follow-up. An exception to this process was when the reporter explicitly stated they were 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 occurred, follow-up was not conducted. Amgen makes a concerted effort to obtain follow-up information. A high-level overview of the Amgen follow-up process for pregnancy reports including flow charts are provided in Appendix 4.

If the available safety information relevant to exposure during pregnancy had represented a safety signal, the signal would have been further evaluated through the Amgen safety governance structure and, if deemed necessary, escalated for consideration of changes to the Reference Safety Information (eg, US Prescribing Information) as well as other forms of risk communication (eg, Dear HCP Letters).

9.6 Bias

This dataset did not include all women who were exposed to Repatha during pregnancy but represents women who reported their Repatha exposure and pregnancy outcomes to Amgen, leading to potential selection bias. For a detailed description of potential biases in this study, please see Section 11. This is a descriptive study in which measures of association were not estimated and data were primarily self-reported. However, during data collection, a differentiation was made between cases that are medically confirmed versus not medically confirmed. At the point of reaching a sufficient number of outcomes, during the subsequent annual report, outcomes will be reported separately for medically confirmed versus not medically confirmed, to assess the potential impact of misclassification of outcomes.

9.7 Study Size

The study size is dependent on the number of reports submitted to the Amgen's Global Safety Database for women exposed to Repatha during pregnancy. A total of 187 cases cumulatively were included in the final analysis cohort for this interim analysis report.

9.8 Data Transformation

Data were extracted from the Amgen's Global Safety Database and followed predefined rules for deriving a final clean analytical file before creation of tables and listings used in this report. Data transformation steps included (1) excluding confirmed paternal exposure cases, (2) excluding cases with Repatha exposure outside of pregnancy window, (3) excluding cases of delivery date before 2015, (4) retaining structured fields, (5) transposing text or narrative field to structured numeric fields by adding additional columns, (6) confirming 1 row per case event, and (7) conducting quality control checks through an additional independent review of 100% of cases.

9.9 Statistical Methods

9.9.1 Main Summary Measures

All analyses were descriptive. Line listings of cases with adverse events were generated and summary numbers and percentages were reported (subject to the final count of Repatha-exposed pregnancies).

9.9.2 Main Statistical Methods

Demographic characteristics of cases were summarized using descriptive statistics. Continuous variables were summarized using the mean, standard deviation (SD), median, and range. Categorical variables were summarized using counts and percentages.

All analyses were descriptive. This study was an exposed case series, thus line listings of pregnancy and maternal complications, pregnancy outcomes, infant outcomes and adverse events were summarized along with tabulations of the numbers and percentages of events. The denominator was the number of pregnancies with exposure to Repatha within 90 days before LMP or during pregnancy and the numerator was the number with the outcome. The proportion with congenital anomalies was estimated in infants of women exposed to Repatha within 90 days before LMP or during pregnancy. The proportion of infants with adverse events observed at 6 months and 12 months of age was estimated. The proportion of mothers who have received Repatha at any time during the pregnancy with pregnancy and maternal complications and adverse events were summarized. Corresponding 95% confidence intervals (CIs) were also presented.

The proportion of infants with adverse events including complications, medical problems or congenital anomalies at birth were assessed in infants of women exposed to Repatha during pregnancy with corresponding 95% CIs. The proportion of infants with adverse events at 6 months and 12 months of age were assessed. All adverse events among mothers who have received Repatha at any time during the pregnancy were 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 were presented, along with corresponding 95% CIs. Due to voluntary reporting, adverse outcomes may be either over- or under-represented; findings cannot be generalized.

9.9.3 Missing Values

All observed data were included, including all reported pregnancies and infant outcomes among women exposed to Repatha during pregnancy. Missing or incomplete data may affect the accuracy of our reporting on the description of the population and outcomes. Missing data were not imputed.

9.9.4 Sensitivity Analyses

Not applicable.

9.9.5 Amendments to the Statistical Analysis Plan

Not applicable.

9.10 Quality Control

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

A quality control check through an additional independent review of 100% of cases was performed during data extraction.

9.11 Changes in Study Conduct

There were no changes in the conduct of the study.

10. RESULTS

A full record of summary tables and listings is provided in Section 15.

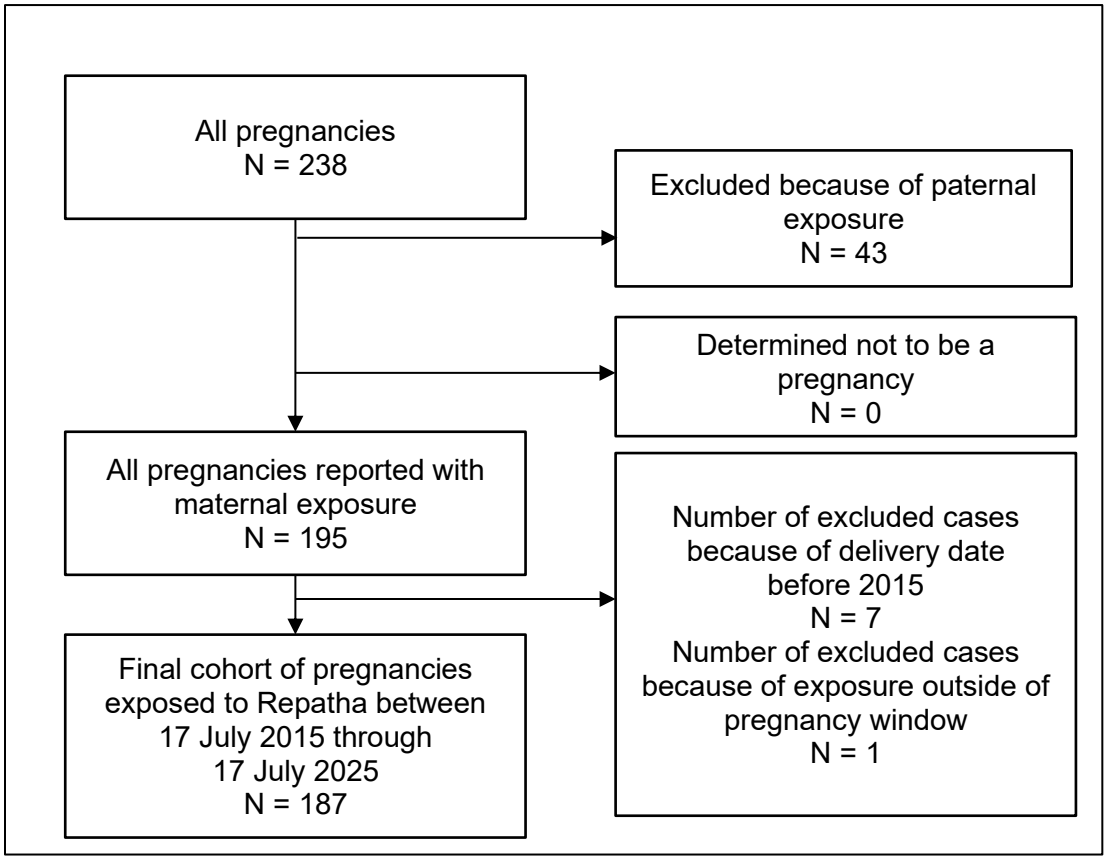
10.1 Participants

In total, 238 pregnancies were reported to have been exposed to Repatha, including 1 twin pregnancy case. Of these 238 cases, 51 pregnancies were excluded because of either paternal exposure (n = 43), delivery date before 2015 (n = 7), or exposure to Repatha outside the pregnancy window (n = 1). After exclusion of these cases, 187 pregnancies had exposure to Repatha from 17 July 2015 through the data cutoff date of 17 July 2025 (Figure 10-1) and were included in the final analysis cohort for this interim analysis report. In comparison to the third interim analysis report, there were 26 new pregnancies exposed to Repatha from 17 July 2024 through 17 July 2025 that met this study's inclusion criteria. Cases in which the inclusion criteria could not be confirmed (eg, missing year of delivery, or missing exposure timing information) were retained in the final study population.

Medically confirmed pregnancies are those reported by HCPs or consumers with evidence of medical records. Because of the small number of reported pregnancies, this interim report did not stratify outcome information by "medically confirmed" versus "maternally reported".

Information on pregnancy and/or infant Repatha exposure from paternal or lactation routes is provided in Section 16.3.4.1 of Periodic Benefit-Risk Evaluation Report (PBRER) Version 19.

Figure 10-1. Attrition - Pregnancies Captured During Annual Follow-up



Count of cases may vary from year-to-year because of case updates and corrections.
Final cohort includes 1 case where the timing of treatment switch from Repatha to Praluent before or during pregnancy is undetermined.
Pregnancy window includes exposure during pregnancy or within 90 days before last menstrual period.
Source: Modified from Table 15-1.

10.2 Descriptive Data

A total of 102 (54.5%) pregnancy cases were medically confirmed. Age at pregnancy was available for 107 (57.2%) cases and unknown for 80 (42.8%) cases (Table 15-2). The median (Q1, Q3) age of mothers at pregnancy was 34.0 (30.0, 38.0) years. Calendar year of delivery was known in 18 (9.6%) pregnancies; calendar year of delivery ranged from 2016 to 2024.

Among the 187 pregnancies, relevant medical history included diabetes (4 cases, 2.1%), thyroid dysfunction (3 cases, 1.6%), difficulty conceiving and hypertension (2 cases each, 1.1%), asthma (1 case, 0.5%), and other (29 cases, 15.5%). Other medical conditions were largely cardiovascular and gastrointestinal-related disorders, but also could include metabolic, respiratory, genitourinary, immunologic, hematologic, neurologic, psychiatric, dermatologic, musculoskeletal, and ophthalmologic conditions.

Previous pregnancy history included live birth (8 cases), spontaneous abortions (7 cases), unknown outcome (4 cases), elective abortion for nonmedical (voluntary) reason (2 cases), and stillbirth (1 case) (Table 15-2).

Among the 187 pregnancies, exposure to concomitant medication during pregnancy was reported for 31 (16.6%) pregnancies (Table 15-2). A by-patient listing of concomitant drugs in the 21 cases that had an adverse event is provided in Listing 15-1. Of the 21 pregnancies with an adverse pregnancy outcome, 7 cases reported concomitant use of ezetimibe, and 6 cases reported at least 1 concomitant medication use of a statin.

Reported maternal or pregnancy complications included gestational diabetes (5 cases), pre-eclampsia/ eclampsia (1 case), and other complications (7 cases) including cardiovascular complications, gestational hypertension, and superficial wound infection from cesarean section (Table 15-3).

10.3 Outcome Data

Pregnancy outcomes were reported as follows (Table 15-4):

- 36 live births
- 14 spontaneous abortions
- 2 elective abortions
- 5 fetal deaths/stillbirths
- 1 pre-term birth
- No fetal or infant congenital anomalies
- 130 unknown/lost to follow-up

In the current interim analysis report 4, one pregnancy that was reported as an elective abortion in the interim report 3 has been reclassified as a spontaneous abortion following clinical review. The case involved a fetal death at the end of the ninth week of gestation, which did not meet the definition of elective termination and was therefore determined to be more accurately categorized as a spontaneous abortion. In total, 2 pregnancies resulted in elective abortion and 5 pregnancies resulted in fetal death/stillbirth as of the data cutoff data (17 July 2025).

10.4 Main Results

10.4.1 Pregnancy Outcomes

A summary of pregnancy outcomes is presented in Table 10-1.

As of the data cutoff date (17 July 2025), among all 187 pregnancies, outcomes for 130 pregnancies were unknown or lost to follow-up; 36 live births were reported including 1 case of a twin birth (of which 7 pregnancies were full-term, 1 was pre-term birth, 1 was post-term birth, and the gestational age was unknown for the remaining 27 pregnancies); 14 pregnancies were spontaneous abortion; 5 were fetal death/stillbirth; and 2 were elective abortion.

Details of the 5 pregnancies that resulted in fetal death or stillbirth, as well as one pre-term birth, are provided below (data on file at Amgen). Almost all cases of fetal death occurred in women with severe cardiovascular disease and/or other major risk factors, and all these cases were medically confirmed.

- A PPD-year-old PPD female patient with homozygous familial hypercholesterolemia and aortic valve replacement became pregnant on an unknown date during participation in an open-label Amgen clinical trial. The patient was receiving Repatha for over 2 years before conception. Repatha was discontinued 1 month after LMP. After 4 months of amenorrhea, the patient was hospitalized because of acute myocardial infarction, recurrent ventricular fibrillation, and cardiogenic shock. Plain balloon angioplasty was performed, and extracorporeal membrane oxygenation was used for cardiopulmonary support. On the next day, gynecological consultation revealed fetal death at PPD gestation. Delivery by cesarean section with hysterectomy was performed. The patient developed cerebral edema and passed away. An autopsy confirmed acute transmural myocardial infarction of the anterior wall, a mechanical complication of the aortic valve prosthesis, and identified cerebral edema as the immediate cause of death. The investigator reported that there was not a reasonable possibility that the events including fetal death were related to Repatha.
- An adult female patient of unknown age with familial hypercholesterolemia became pregnant while receiving Repatha and lost her pregnancy (preferred term [PT]: fetal death) on an unknown date. The duration of Repatha exposure is unknown. No more information is available as the reporting physician declined consent for follow-up.
- A PPD-year-old female patient with homozygous familial hypercholesterolemia and low-cholesterol diet became pregnant in PPD 2016 during participation in a Repatha clinical trial. The patient was receiving Repatha for over 2 years before conception. The patient was diagnosed with aortic valve stenosis and aortic arch

dilatation in 2015 and treated using the Bentall method (aortic valve and part of the ascending aorta was replaced with a prosthesis). Permanent anticoagulation with warfarin was introduced into pharmacotherapy. Post pregnancy, all hypolipidemic drugs were discontinued and warfarin was replaced with heparin. The plasma concentration of total cholesterol was 15.9 mmol/L (preconception median value was 3.99 mmol/L) in the 19th week of pregnancy. On an unknown date in PPD (PPD gestation), the patient suddenly developed shortness of breath and pain in the lumbar region and passed away because of cardiac arrest. This was caused by thrombosis of the aortic valve prosthesis, which caused myocardial ischemia. Despite intensive medical care, the life of the fetus could not be saved. The authors of this literature report did not provide an assessment of a causal relationship between Repatha and the fetal death.

- A PPD-year-old female patient with heterozygous familial hypercholesterolemia and family history of early onset coronary artery disease became pregnant on an unknown date during participation in a postmarketing noninterventional clinical trial. From PPD 2020 to PPD 2022, the patient's fasting high density lipoprotein cholesterol levels were between 72 to 100 mg/dl and fasting LDL between 77 to 203 mg/dl. The patient received the last dose of Repatha on PPD 2021. The reason for discontinuation was reported as improvement of baseline condition. The pregnancy ended in fetal death of an unknown cause on PPD. The investigator reported that there was not a reasonable possibility that the fetal death was related to Repatha.
- A PPD-year-old female patient with a history of PPD and untreated familial hypercholesterolemia started Repatha when she was approximately PPD pregnant. During the PPD of her pregnancy, she contracted COVID-19, which led to a diagnosis of ST-elevated myocardial infarction (STEMI) (in leads II, III, and augmented Vector Foot [aVF]). Emergency coronary angiography revealed a total occlusion of the distal left circumflex artery. The patient underwent thrombectomy followed by the placement of an everolimus-eluting stent. Subsequently, the patient had thrombolysis in myocardial infarction (TIMI) grade 3. On the 11th day of hospitalization, she was discharged in stable condition with evolocumab, ezetimibe, and standard dual antiplatelet therapy. A month later, prasugrel was discontinued due to anticipated labor and bleeding risk. On an

unspecified date, the patient presented to the hospital with amniotic fluid leakage and abdominal pain, where fetal heartbeats were not detected, and a stillborn fetus was delivered. According to the American College of Obstetricians and Gynecologists, fetal death or stillbirth is defined as the death of a fetus at 20 weeks gestation or later. The available information does not confirm whether the gestation was ≥ 20 weeks at the time of pregnancy loss. The fetal death could be influenced by multiple factors, including known serious coronary risk factors, potential plaque rupture acceleration due to COVID 19, myocardial infarction during the organogenetic period of pregnancy, percutaneous coronary intervention, concomitant medications like ezetimibe and prasugrel, and advanced maternal age.

- A PPD-year-old female patient with a history of PPD (diagnosed on PPD), PPD , hypercholesterolemia, PPD was receiving off-label Repatha (evolocumab) 420 mg twice monthly via on-body injector. She had previously discontinued Repatha 1.5 years earlier due to pregnancy and breastfeeding. On PPD 2022, Repatha was again discontinued upon confirmation of pregnancy. During this pregnancy, the patient was taking insulin, Wellbutrin, Mounjaro, labetalol hydrochloride, progesterone and prenatal vitamins as concomitant medications. On PPD 2023, she developed pre-eclampsia, and on PPD 2023, at PPD and PPD of gestation, she delivered a live PPD infant. The neonate was diagnosed with respiratory distress syndrome (RDS), and gastroesophageal reflux disease (GERD), requiring 54 days of neonatal intensive care unit care. The patient did not breastfeed while on Repatha, and no treatment details were provided. The outcome of pre-eclampsia was reported as recovered/resolved. No causal relationship between pre-eclampsia, premature delivery, and Repatha was reported. as per available information, the infant had growth curves and developmental milestones as expected for chronological age. The patient did not breastfeed while being on Repatha. No other treatment information was available.

Table 10-1. Pregnancy Outcomes Collected From Healthcare Provider or Consumer-reported Information

	Pregnancies Exposed to Repatha N = 187	
Pregnancy Outcomes	n	% (95% CI)
Unknown/Lost to follow-up	130	69.52 (62.38, 76.03)
Live births	36	19.25 (13.86, 25.64)
Full-term births[a]	7	19.44 (8.19, 36.02)
Pre-term births[b]	1	2.78 (0.07, 14.53)
Post-term births[c]	1	2.78 (0.07, 14.53)
Other live births[d]	27	75.00 (57.80, 87.88)
Number of live births		
Singleton	28	77.78 (60.85, 89.88)
Twin	1	2.78 (0.07, 14.53)
Unknown	7	19.44 (8.19, 36.02)
Spontaneous abortion (among all pregnancies)	14	7.49 (4.15, 12.24)
Elective abortion (among all pregnancies)	2	1.07 (0.13, 3.81)
Fetal death/stillbirth (among all pregnancies)	5	2.67 (0.87, 6.13)
Birth weight known	11	5.88 (2.97, 10.28)
Birth weight in grams (median (Q1, Q3))	3400.00	(2840.00, 3945.00)
Baby born with a congenital anomaly (among live birth pregnancies)	0	0.00 (- , -)

NEC = Not elsewhere classified.
Pregnancy outcome categories are not mutually exclusive.
There may be duplication of a case with the outcome of fetal death that was reported from a CT in the previous report and from scientific literature this year. The cases are in further review and may lead to correction in the next interim report.
[a] Full-term births are defined by the following categories from the birth outcome field: Full Term Delivery NOS, Term w/o complication, Term w Congenital Anomaly. Includes 1 early-term delivery.
[b] Pre-term births are defined by the following categories from the birth outcome field: Pre-Term birth NOS, Pre-Term birth w/o Complications, Pre-Term Birth with complications.
[c] Post-term births are defined by cases with the birth outcome: Post-Term w/o Complications.
[d] Other live births are those not otherwise defined in Full-term, Pre-term and Post-Term births. Other live births may include the following categories from the birth outcome field: Delivered NOS, Live birth NOS, Live birth, normal, Lost to Follow Up, or Spontaneous Abortion NOS.
Source: Modified from Table 15-4.

10.4.2 Infant Outcomes

Out of the 36 live births including 1 twin birth, there were no reported events of abnormal screening tests, abnormal growth curves/delayed developmental milestones, or persistent health problems either at ≤ 6 months or at ≤ 12 months of age (Table 15-5).

Birth weight was known in 11 pregnancies, with the median (Q1, Q3) birth weight of 3400.0 (2840.0, 3945.0) grams. No congenital anomalies were reported in these 36 live birth outcome cases (Table 15-4).

10.5 Other Analyses

Not applicable.

10.6 Adverse Events/Adverse Reactions

A summary of Repatha exposure during pregnancy and outcomes among cases that had an adverse event is provided in Listing 15-1.

Of the 21 pregnancies that ended in spontaneous abortion, elective termination, or fetal death/ stillbirth, 15 (71.4%) were medically confirmed pregnancies. The median (Q1, Q3) age of the mother was 35.0 (30.0, 39.0) years among those with available ages (n=16). Eight cases reported concomitant drug use, among which 7 cases reported concomitant use of ezetimibe, and 6 cases reported at least 1 concomitant medication use of a statin (Listing 15-1).

11. DISCUSSION

11.1 Key Results

From 17 July 2015 to 17 July 2025, 187 pregnancies were reported in the Amgen's Global Safety Database that had maternal exposure to Repatha, of which pregnancy outcomes were known in 57 pregnancies. Pregnancy outcomes included: 36 live births, 14 spontaneous abortions, 5 fetal deaths/stillbirths, and 2 elective abortions. No cases of congenital anomalies, abnormal growth curves, delayed developmental milestones, premature delivery, abnormal screening tests, or persistent health problems in the infants were reported. Maternal or pregnancy complications recorded in the database included gestational diabetes (5 cases), pre-eclampsia/ eclampsia (1 case), and other complications (7 cases) such as cardiovascular complications, gestational hypertension, and superficial wound infection from cesarean section.

11.2 Limitations

This dataset did not include all women who were exposed to Repatha during pregnancy but represents women who reported their Repatha exposure and pregnancy outcomes to the Amgen's Global Safety Database, leading to potential selection bias. These women may be different than women who did not report their exposure as women with adverse events are more likely to report their exposure and recall them more accurately than women without adverse events, leading to potential reporting and recall bias, particularly with retrospective data collection (Choi and Pak, 2005; Werler et al, 1989). Consequentially, adverse pregnancy and infant outcomes may be overestimated. In contrast, there may also be potential underreporting of spontaneous abortion, a limitation not unique to this study, as early gestational age fetal losses may occur before pregnancy status is confirmed (Food and Drug Administration, 2005).

Data derived from spontaneous reporting systems may have missing demographic and clinical information (eg, missing age, comorbidities, and concomitant medications). Indeed, in this study there was evidence of missing data, for example age at pregnancy was missing for 42.8% cases. The lack of clinical information limits the ability to assess confounding factors in these case reports.

Exposure to Repatha during pregnancy is very infrequent. In the previous pregnancy registry feasibility report submitted to FDA (Pregnancy Registry Feasibility Report; 09 September 2019), utilizing data from 2 large and nationally representative commercial claims healthcare databases representative of the working population (18 to 65 years of age) in the US and a nationally representative primary care dataset

from the United Kingdom, there was no Repatha exposure identified during pregnancy and only 1 exposure identified within 180 days before the estimated LMP date. Therefore, despite the limitations of the spontaneous reporting data system, this data source enabled the identification and assessment of over 100 exposed pregnancies, which was not possible in either a secondary data source or a prospective pregnancy registry.

11.3 Interpretation

During the 10-year reporting period from 17 July 2015 to 17 July 2025, 187 women reported maternal exposure to Repatha during pregnancy in the spontaneous reporting system. Though exposure to Repatha among women of childbearing age is uncommon, patients with familial hypercholesterolemia tend to be diagnosed at younger ages representing greater maternal risk during pregnancy and lactation (Bláha et al, 2022).

Cumulatively, since the International Birth Date of Repatha (17 July 2015) up to the end of the current reporting period (17 July 2025), an estimated 2 884 294 female patients have been exposed to Repatha globally in the postmarketing setting, of which 25 919 were < 35 years and 210 009 were between 35 to 49 years (PBRER Version 19).

Women exposed to Repatha before or during pregnancy identified for this report were all indicated to receive Repatha, and thus this patient population had known baseline cardiovascular medical conditions and can be largely predisposed to health risks. Pregnant women with cardiac disease have increased risk of pregnancy complications including pre-term labor, pre-eclampsia, and postpartum hemorrhage, with offspring complications occurring in 18% to 30% of patients with heart disease (Roos-Hesselink et al, 2019; Regitz-Zagrosek et al, 2018). Overall, maternal heart disease complications occur in between 1% and 4% of pregnancies and accounts for up to 15% of maternal deaths (Regitz-Zagrosek et al, 2018; Knight et al, 2017).

A total of 5 out of 21 cases that had an adverse pregnancy outcome were enrolled in an Amgen clinical study and 4 out of 21 cases were enrolled in a postmarketing noninterventional study with an investigational product (data on file at Amgen). Of the 21 pregnancies with an adverse pregnancy outcome, 7 cases reported concomitant use of ezetimibe and 6 cases reported at least 1 concomitant medication use of a statin. Statins are understood to be contraindicated in pregnancy and recommended to be avoided during pregnancy because of the potential risk of a congenital anomaly from the statin exposure (Karalis et al, 2016).

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. In the US general population, the estimated background risk of major birth defects is 2% to 4%, elective abortion approximately 19%, and spontaneous abortion between 15% to 20% (Mahadevan et al, 2022; Centers for Disease Control and Prevention, 2008; Food and Drug Administration, 2005; Repatha Prescribing Information). Overall, few outcomes of maternal and pregnancy complications were reported, and no fetal defects were reported. A review of all pregnancy cases, including pregnancy outcomes and adverse events received did not reveal any patterns suggesting a safety concern.

This study uses alternative methodology and excludes events that occurred before 17 July 2015, which may lead to numerical differences in comparison with cumulative counts in the PBRER Version 19 with the same data lock point.

11.4 Generalizability

This was a global study inclusive of reports from the worldwide population. However, given the potential reporting bias, the findings of this study may not be generalizable to all pregnant women exposed to Repatha.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSION

Based on available data as of the data cutoff date of 17 July 2025, there are no safety concerns identified. Interpretation of data is limited by high rate of missing outcome data. However, these conclusions remain preliminary till final study report submission in Sep 2026. Amgen will continue to monitor Repatha safety in pregnant women.

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15. SUMMARY TABLES, FIGURES, AND LISTING

Table 15-1. Attrition - Pregnancies Captured During Annual Follow-up

Criteria Description	Cases Excluded	Cases Remaining[a]
Total reported cases[b]	0	238
Excluded due to paternal exposure	43	195
Determined not to be a pregnancy	0	195
All pregnant women reported with maternal exposure	0	195
Number of excluded cases due to delivery date before 2015	7	188
Number of excluded cases due to exposure outside of pregnancy window[c]	1	187
Final cohort of confirmed pregnancy exposed to Repatha between July 2015 and July 17, 2025	0	187

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[a] Count of cases may vary from year-to-year due to case updates and corrections.
[b] Final cohort includes one case where the timing of treatment switch from Repatha to Praluent before or during pregnancy is undetermined.
[c] Pregnancy window includes exposure during pregnancy or within 90 days prior to last menstrual period.

Program: /userdata/cfor/projects/p25_pv_120/saspgms/04_tbl_15_1.sas
Output: t15-01-attrition.rtf (Date generated: 05AUG2025:13:01) Source data: repathapmr_dt17jul2025_final.sas7bdat

Table 15-2. Maternal Demographics and History

Case Characteristics	Number of Cases N = 187 n (%)
Medically Confirmed	102 (54.55)
Age at pregnancy (median (Q1, Q3))	34.00 (30.00, 38.00)
18 - 30 years	27 (14.44)
31 - 34 years	35 (18.72)
35 - 40 years	33 (17.65)
41 - 50 years	9 (4.81)
51+ years	3 (1.60)
Missing	80 (42.78)
Year of delivery[a]	
2015	0 (0.00)
2016	2 (1.07)
2017	2 (1.07)
2018	6 (3.21)
2019	1 (0.53)
2020	2 (1.07)
2021	2 (1.07)
2022	1 (0.53)
2023	1 (0.53)
2024	1 (0.53)
2025	0 (0.00)
Missing	169 (90.37)
Clinical Characteristics	
Medical history recorded	
Hypertension	2 (1.07)
Seizure	0 (0.00)

Maternal characteristics will be captured in all pregnancies (ongoing and complete) during each annual follow-up.

[a] Only for complete pregnancies. Sum may not equal the total exposed pregnancies.

[b] Other medical history conditions included cardiovascular, gastrointestinal, metabolic, respiratory, genitourinary, immunologic, hematologic, neurologic, psychiatric, dermatologic, musculoskeletal and ophthalmologic conditions.

Program: /userdata/cfor/projects/p25_pv_120/saspgms/04_tbl_15_2.sas

Output: t15-02-maternal-demographics-history.rtf (Date generated: 05AUG2025:13:02) Source data: repathapmr_dt17jul2025_final.sas7bdat

Table 15-2. Maternal Demographics and History

Case Characteristics	Number of Cases N = 187 n (%)
Diabetes	4 (2.14)
Difficulty conceiving	2 (1.07)
Asthma	1 (0.53)
Thyroid dysfunction	3 (1.60)
Other[b]	29 (15.51)
Exposed to concomitant medication during pregnancy	31 (16.58)
Previous pregnancy history	
Live birth pregnancies	8 (4.28)
Stillbirths	1 (0.53)
Spontaneous abortions	7 (3.74)
Pregnancy resulting in a birth defect/complication	0 (0.00)
Elective abortions	
Induced for medical reason	0 (0.00)
Induced for non-medical (voluntary) reason	2 (1.07)
Pregnancies with unknown outcomes	4 (2.14)

Maternal characteristics will be captured in all pregnancies (ongoing and complete) during each annual follow-up.

[a] Only for complete pregnancies. Sum may not equal the total exposed pregnancies.

[b] Other medical history conditions included cardiovascular, gastrointestinal, metabolic, respiratory, genitourinary, immunologic, hematologic, neurologic, psychiatric, dermatologic, musculoskeletal and ophthalmologic conditions.

Program: /userdata/cfor/projects/p25_pv_120/saspgms/04_tbl_15_2.sas

Output: t15-02-maternal-demographics-history.rtf (Date generated: 05AUG2025:13:02) Source data: repathapmr_dt17jul2025_final.sas7bdat

Table 15-3. Maternal and Pregnancy Complications

Complications	Number of Cases N = 187 n	% (95% CI)
Pre-eclampsia/ Eclampsia	1	0.53 (0.01, 2.94)
Gestational diabetes	5	2.67 (0.87, 6.13)
Placenta praevia	0	0.00 (- , -)
Molar	0	0.00 (- , -)
Ectopic	0	0.00 (- , -)
Other[a]	7	3.74 (1.52, 7.56)

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Maternal characteristics will be captured in all pregnancies (ongoing and complete) during each annual follow-up.

[a] Other complications included cardiovascular complications, gestational hypertension and superficial wound infection from cesarean section.

Program: /userdata/cfor/projects/p25_pv_120/saspgms/04_tbl_15_3.sas

Output: t15-03-maternal-and-pregnancy-complications.rtf (Date generated: 05AUG2025:13:04) Source data: repathapmr_dt17jul2025_final.sas7bdat

Table 15.4. Pregnancy Outcomes Collected from Healthcare Provider or Consumer-reported Information

Pregnancy Outcomes	Pregnancies Exposed to Repatha N = 187 n	% (95% CI)
Unknown/Lost to follow-up	130	69.52 (62.38, 76.03)
Live births	36	19.25 (13.86, 25.64)
Full-term births[a]	7	19.44 (8.19, 36.02)
Pre-term births[b]	1	2.78 (0.07, 14.53)
Post-term births[c]	1	2.78 (0.07, 14.53)
Other live births[d]	27	75.00 (57.80, 87.88)
Number of live births		
Singleton	28	77.78 (60.85, 89.88)
Twin	1	2.78 (0.07, 14.53)
Unknown	7	19.44 (8.19, 36.02)
Spontaneous abortion (among all pregnancies)	14	7.49 (4.15, 12.24)
Elective abortion (among all pregnancies)	2	1.07 (0.13, 3.81)
Fetal death/stillbirth (among all pregnancies)	5	2.67 (0.87, 6.13)
Birth weight known	11	5.88 (2.97, 10.28)
Birth weight in grams (median (Q1, Q3))	3400.00	(2840.00, 3945.00)
Baby born with a congenital anomaly (among live birth pregnancies)	0	0.00 (- , -)
Congenital anomaly type		
Cardiac and vascular disorders	0	0.00 (- , -)
Ear and labyrinthine disorders	0	0.00 (- , -)
Endocrine disorders	0	0.00 (- , -)
Eye disorders	0	0.00 (- , -)
Gastrointestinal tract disorders	0	0.00 (- , -)
Hepatobiliary disorders	0	0.00 (- , -)

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NEC = Not elsewhere classified.
Pregnancy outcome categories are not mutually exclusive.
There may be duplication of a case with the outcome of fetal death that was reported from a CT in the previous report and from scientific literature this year. The cases are in further review and may lead to correction in the next interim report.
[a] Full-term births are defined by the following categories from the birth outcome field: Full Term Delivery NOS, Term w/o complication, Term w Congenital Anomaly. Includes 1 early-term delivery.
[b] Pre-term births are defined by the following categories from the birth outcome field: Pre-Term birth NOS, Pre-Term birth w/o Complications, Pre-Term Birth with complications.
[c] Post-term births are defined by cases with the birth outcome: Post-Term w/o Complications.
[d] Other live births are those not otherwise defined in Full-term, Pre-term and Post-Term births. Other live births may include the following categories from the birth outcome field: Delivered NOS, Live birth NOS, Live birth, normal, Lost to Follow Up, or Spontaneous Abortion NOS.
Program: /userdata/cfor/projects/p25_pv_120/saspgms/04_tbl_15_4.sas
Output: t15-04-pregnancy-outcomes.rtf (Date generated: 15AUG2025:15:10) Source data: repathapmr_dt17jul2025_final.sas7bdat

Table 15.4. Pregnancy Outcomes Collected from Healthcare Provider or Consumer-reported Information

Pregnancy Outcomes	Pregnancies Exposed to Repatha N = 187	
	n	% (95% CI)
Musculoskeletal and connective tissue disorders	0	0.00 (- , -)
Neurological disorders	0	0.00 (- , -)
Renal and urinary tract disorders	0	0.00 (- , -)
Reproductive tract and breast disorders	0	0.00 (- , -)
Respiratory disorders	0	0.00 (- , -)
Congenital and hereditary disorders NEC	0	0.00 (- , -)

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NEC = Not elsewhere classified.
Pregnancy outcome categories are not mutually exclusive.
There may be duplication of a case with the outcome of fetal death that was reported from a CT in the previous report and from scientific literature this year. The cases are in further review and may lead to correction in the next interim report.
[a] Full-term births are defined by the following categories from the birth outcome field: Full Term Delivery NOS, Term w/o complication, Term w Congenital Anomaly. Includes 1 early-term delivery.
[b] Pre-term births are defined by the following categories from the birth outcome field: Pre-Term birth NOS, Pre-Term birth w/o Complications, Pre-Term Birth with complications.
[c] Post-term births are defined by cases with the birth outcome: Post-Term w/o Complications.
[d] Other live births are those not otherwise defined in Full-term, Pre-term and Post-Term births. Other live births may include the following categories from the birth outcome field: Delivered NOS, Live birth NOS, Live birth, normal, Lost to Follow Up, or Spontaneous Abortion NOS.
Program: /userdata/cfor/projects/p25_pv_120/saspgms/04_tbl_15_4.sas
Output: t15-04-pregnancy-outcomes.rtf (Date generated: 15AUG2025:15:10) Source data: repathapmr_dt17jul2025_final.sas7bdat

Table 15-5. Infant Outcomes

	Total Infants N = 36			
	<=6 Months Post Delivery		<=12 Months Post Delivery	
Outcome	n	% (95% CI)	n	% (95% CI)
Abnormal screening tests for infant	0	0.00 (- , -)	0	0.00 (- , -)
Abnormal growth curves/delayed developmental milestones	0	0.00 (- , -)	0	0.00 (- , -)
Persistent health problems in infant	0	0.00 (- , -)	0	0.00 (- , -)

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Program: /userdata/cfor/projects/p25_pv_120/saspgms/04_tbl_15_5.sas
Output: t15-05-infant-outcomes.rtf (Date generated: 15AUG2025:15:12) Source data: repathapmr_dt17jul2025_final.sas7bdat

Listing 15-1. Summary of Repatha Exposure Duration and Other Characteristics for Individuals Who Reported an Adverse Pregnancy Outcome

Pregnancy Case Number	Patient Age	Medically Confirmed	Dosage Regimen Start Date	Dosage Regimen Stop Date	Concomitant Drugs	Adverse Pregnancy Outcome
PPD		Yes	PPD /2016	Unknown	Lasix, Bisoprolol, Aldactone, Pantomed, Dafalgan, Ezetrol, Crestor, Asaflow, Zyrtec	Spontaneous abortion or miscarriage
		Yes	PPD /2014	Unknown	Ezetimibe, Atorvastatin, Macrodantin, Citalopram, Thyroxine	Spontaneous abortion or miscarriage
		Yes	Unknown	Unknown	-	Spontaneous abortion or miscarriage
		No	PPD /2022	Unknown	-	Spontaneous abortion or miscarriage
		Yes	PPD /2013	PPD /2016	Warfarin, Acetylsalicylic Acid, Rosuvastatin, Omeprazole, Bisoprolol, Ezetimibe, Alteplase, Noradrenalin, Metronidazole	Fetal death or stillbirth

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The median age (Q1, Q3) of cases is 35.00 (30.00,39.00) among cases (n = 16) with available ages.
Pregnancy outcome categories are not mutually exclusive.
Program: /userdata/cfor/projects/p25_pv_120/saspgms/05_listing_15_1.sas
Output: l15-01-listing.rtf (Date generated: 05AUG2025:13:19) Source data: repathapmr_dt17jul2025_final.sas7bdat

Listing 15-1. Summary of Repatha Exposure Duration and Other Characteristics for Individuals Who Reported an Adverse Pregnancy Outcome

Pregnancy Case Number	Patient Age	Medically Confirmed	Dosage Regimen Start Date	Dosage Regimen Stop Date	Concomitant Drugs	Adverse Pregnancy Outcome
PPD		Yes	PPD /2013	Unknown	-	Spontaneous abortion or miscarriage
		Yes	PPD /2013	PPD /2018	Ezetimibe, Rosuvastatin	Spontaneous abortion or miscarriage
		Yes	PPD /2017	Unknown	Ezetrol, Rosucard	Spontaneous abortion or miscarriage
		Yes	PPD /2013	PPD /2016	Heparin, Warfarin	Fetal death or stillbirth
		Yes	PPD /2013	PPD /2016	-	Spontaneous abortion or miscarriage
		No	Unknown	Unknown	-	Spontaneous abortion or miscarriage
		Yes	Unknown	Unknown	-	Elective abortion
		No	PPD /2019, PPD /2021	Unknown	-	Spontaneous abortion or miscarriage
		Yes	PPD /2020	PPD /2021	Zetia, Cholebine, Thyradin, Crestor	Fetal death or stillbirth

The median age (Q1, Q3) of cases is 35.00 (30.00,39.00) among cases (n = 16) with available ages.
Pregnancy outcome categories are not mutually exclusive.
Program: /userdata/cfor/projects/p25_pv_120/saspgms/05_listing_15_1.sas
Output: l15-01-listing.rtf (Date generated: 05AUG2025:13:19) Source data: repathapmr_dt17jul2025_final.sas7bdat

Listing 15-1. Summary of Repatha Exposure Duration and Other Characteristics for Individuals Who Reported an Adverse Pregnancy Outcome

Pregnancy Case Number	Patient Age	Medically Confirmed	Dosage Regimen Start Date	Dosage Regimen Stop Date	Concomitant Drugs	Adverse Pregnancy Outcome
PPD		Yes	PPD /2023	Unknown	Prasugrel, Ezetimibe	Fetal death or stillbirth
		Yes	Unknown	Unknown	-	Spontaneous abortion or miscarriage
		Yes	PPD /2013	Unknown	-	Elective abortion
		No	Unknown	Unknown	-	Spontaneous abortion or miscarriage
		Yes	Unknown	Unknown	-	Fetal death or stillbirth
		No	Unknown	Unknown	-	Spontaneous abortion or miscarriage
		No	Unknown	Unknown	-	Spontaneous abortion or miscarriage

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The median age (Q1, Q3) of cases is 35.00 (30.00,39.00) among cases (n = 16) with available ages.
Pregnancy outcome categories are not mutually exclusive.
Program: /userdata/cfor/projects/p25_pv_120/saspgms/05_listing_15_1.sas
Output: l15-01-listing.rtf (Date generated: 05AUG2025:13:19) Source data: repathapmr_dt17jul2025_final.sas7bdat

16. ANNEXES

Annex 1. List of Stand-alone Documents

Not Applicable

Annex 2. Study Protocol and Amendments

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

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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 gen 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.

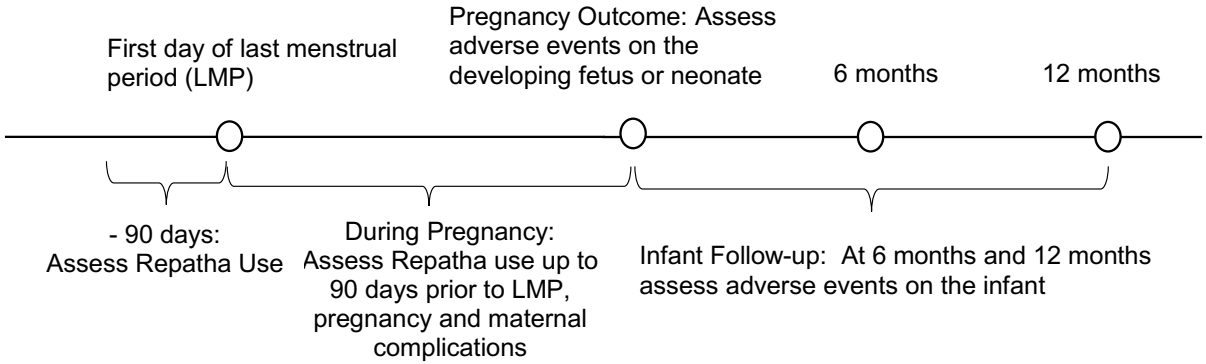
This document must not be disclosed to anyone other than the site study staff and members of the Institutional Review Board/Independent Ethics Committee/Institutional Scientific Review Board or equivalent, as applicable.

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

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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

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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 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

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

SIX AND TWELVE MONTH INFANT QUESTIONNAIRE

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_____

AMGEN®

Annex 3. Signature of Coordinating Investigator

Investigator Signature

STUDY NUMBER: 20200408

STUDY REPORT TITLE: An Observational Case Series to Describe Women Exposed to Repatha During Pregnancy and Infant Outcomes During the First Year of Life.

I have read the above named Observational Research Study Report and signify my agreement with the overall conclusions.

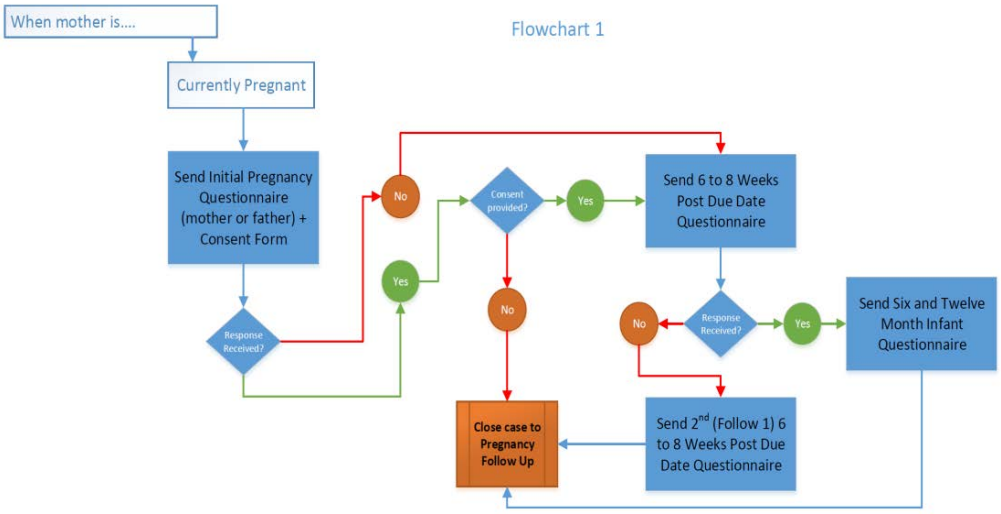
Name of Investigator or Coordinating Investigator:	PPD
Institution Name and Address:	Amgen Inc.
	1 Amgen Center Dr, Thousand Oaks, CA 91320
Signature of Investigator:	PPD
Date:	09/09/2025

Annex 4. Additional Information

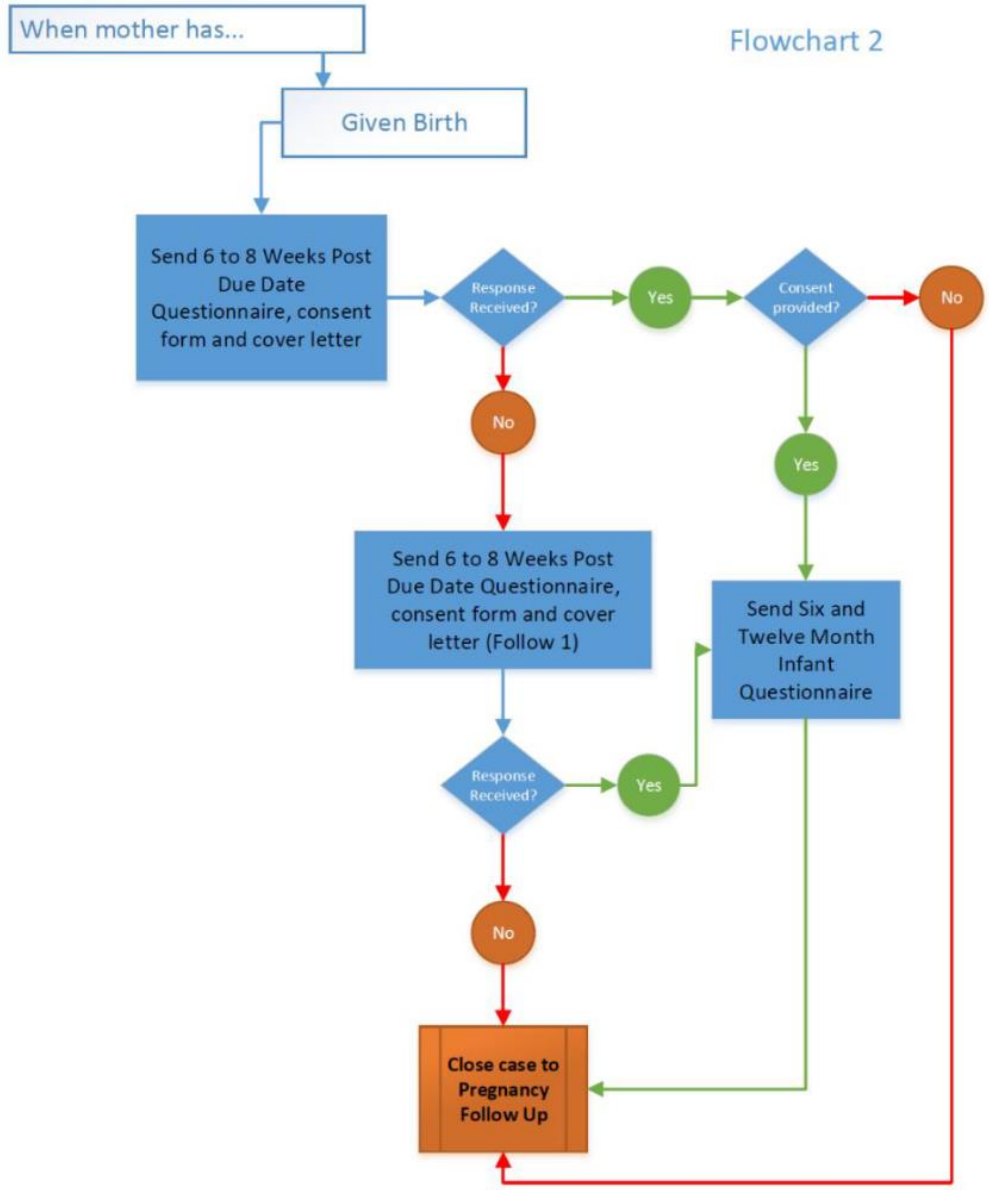
FDA comment: We note that a significant number of pregnancies are lost to follow up. You should make a concerted effort to improve the follow-up rate.

Response: With regards to concerted efforts on improving the lost to follow-up rate, we want to reassure FDA that Amgen has a comprehensive follow-up and due diligence process for case reports involving Repatha exposure during pregnancy. In alignment with industry standard and regulatory expectations, Amgen ensure a robust follow up approach is followed. Our pharmacovigilance process includes initiating a targeted follow up at the time of initial report receipt to obtain critical information such as gestational age at exposure, duration and timing of drug use, relevant medical obstetric history and outcome for both mother and fetus. Amgen follows a clear step-by-step follow up process based on type of case report—whether the person is currently pregnant, has given birth, or had a miscarriage. Below is the high-level process flows. We start by making two phone follow-up attempts, conducted on separate days. If there is no response, we proceed by sending out an initial questionnaire and consent form, and if we don't hear back, we send a second follow-up. When we do receive a response by phone, we send the forms as well—provided we have the patient's consent to share additional information. For birth cases, we also check in again at 6–8 weeks and later at 6 and 12 months to collect more information. Since pregnancy exposure case reporting and follow-up through the infant's first year of life were voluntary reporting, patients were free to withdraw their consent at any time. Amgen will continue to make a concerted effort to gather follow up information on pregnancy exposure case.

Flow Chart 1: Follow up for cases where mother is currently pregnant



Flow Chart 2: Follow up for cases where mother has given birth – Post-delivery



Flow Chart 3: Follow up for Miscarriage/Spontaneous Abortion Cases