## Summary Table of Study Protocol

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|---|---|
| **Title** | A Multinational Observational Study to Evaluate the Safety of Repatha® in Pregnancy |
| **Protocol version identifier** | **2.0** |
| **Date of last version of the protocol** | 17 May 2016 |
| **EU Post Authorisation Study (PAS) Register No** | **EUPAS15153** |
| **NCT Number** | **NCT02906124** |
| **Active Substance** | Evolocumab |
| **Medicinal Product** | Repatha® |
| **Product Reference** | EU/1/15/1016 |
| **Procedure Number** | EMA/H/C/3766 |
| **Marketing Authorisation Holder(s)** | Amgen Europe B.V. |
| **Joint PASS** | No |
| **Research Question and Objectives** | Research Question: To evaluate **pregnancy and infant** outcomes **among** females diagnosed with familial hypercholesterolaemia (FH), exposed to Repatha® during pregnancy. This includes follow-up of their infants to the age of 12 months.<br>Primary Objective: To describe congenital anomalies in infants of females with FH exposed to Repatha® within 15 weeks prior to or during pregnancy, followed to the age of 12 months.<br>Secondary Objectives: To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to and/or during pregnancy; To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to and/or during pregnancy; To describe **health and developmental** outcomes in infants up to the age of 12 months, born to females diagnosed with FH **and exposed/unexposed to Repatha® during pregnancy and/or breastfeeding.** |
| **Countries of Study** | Europe (multicountry), South Africa, Australia |
| **Author** | PPD<br>Amgen Ltd<br>**1 Uxbridge Business Park**<br>**Sanderson Road**<br>**Uxbridge UB8 1DH**<br>UK |

**Marketing Authorisation Holder**

| | |
|---|---|
| **Marketing authorisation holder(s)** | Amgen Europe B.V. |
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## Confidentiality Notice

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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.

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**Investigator's Agreement**

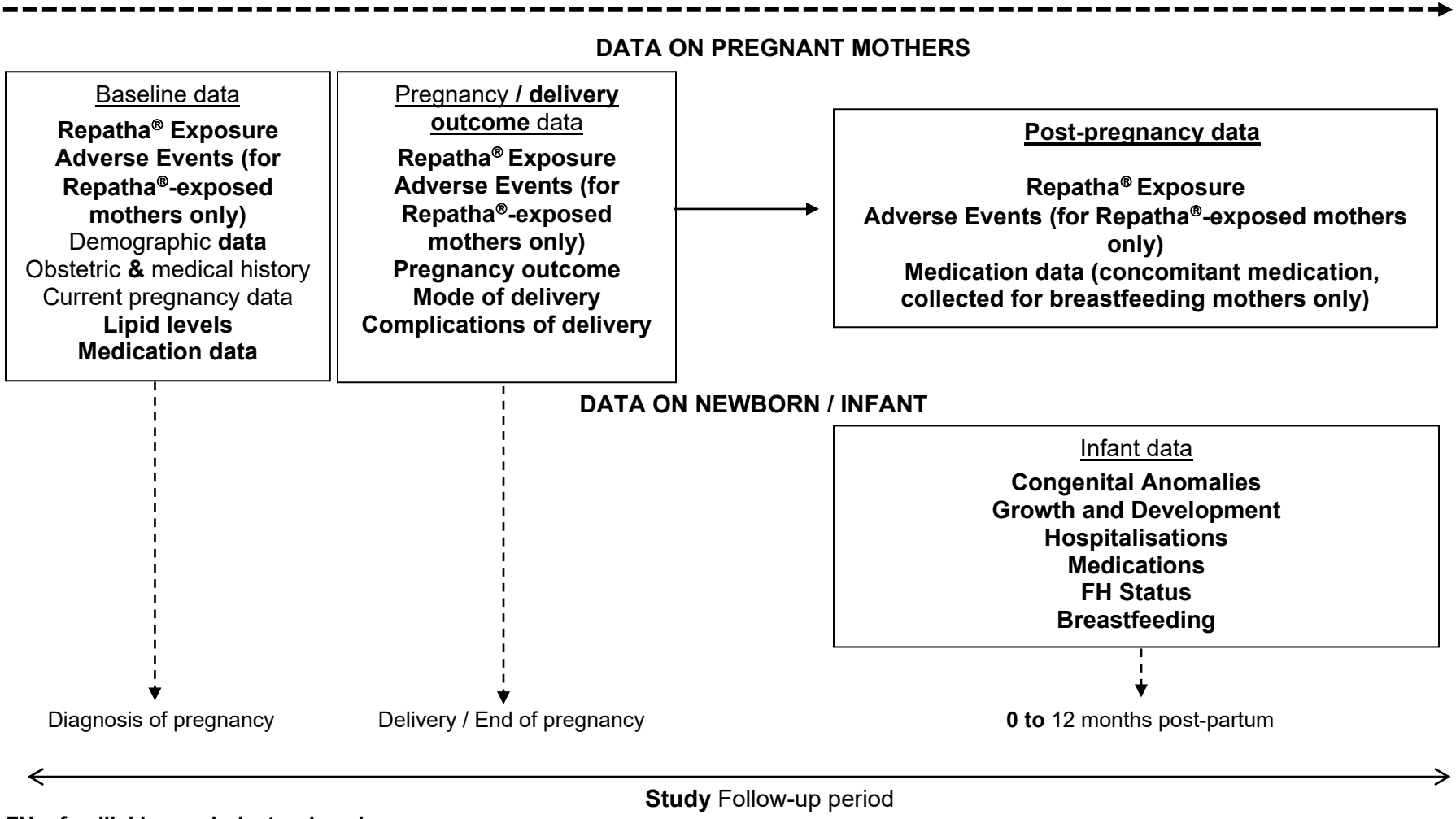
I have read the attached protocol entitled "A Multinational Observational Study to Evaluate the Safety of Repatha® in Pregnancy", dated **18 December 2018**, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

| | |
|---|---|
| Signature | |
| Name of Investigator | Date (DD Month YYYY) |

**Study Design Schema**

Enrolment **occurs** at **the** time of identification **of the pregnancy** by **the** study site




**FH = familial hypercholesterolaemia**

## 1. Table of Contents

**List of Appendices**

## 2. List of Abbreviations

| Abbreviation | Meaning |
|---|---|
| CA | Competent Authority |
| CETP | Cholesterylester transfer protein |
| eCRF | Electronic case report form |
| EMA | European Medicines Authority |
| ENCePP | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| Enrolment | Subject is considered enrolled when informed consent/notification has occurred (if applicable according to local requirements), eligibility has been determined and data entry initiated into the eCRF. |
| EU PAS | European Post-Authorisation Study |
| EUROCAT | European Surveillance of Congenital Anomalies |
| FH | Familial hypercholesterolaemia |
| ICD10-BPA | International Classification of Diseases version 10 British Paediatric Association |
| ICH GCP | International Committee for Harmonisation Good Clinical Practice |
| ICJME | International Committee of Medical Journal Editors |
| IgG | Immunoglobulin G |
| IRB/IEC | Institutional Review Board/ Institutional Ethics Committee |
| LDL-C | Low density lipoprotein-cholesterol |
| MAN | Manual |
| PCSK9 | Proprotein convertase subtilisin/kexin type 9 |
| SmPC | Summary of Product Characteristics |
| SOP | Standard Operating Procedure |
| Source data | Information from an original record or certified as a copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents (original records or certified copies). (ICH Guideline E6). |
| Study start | Date on which first study site is initiated |
| QM | Once-monthly |

## 3. Responsible Parties

Amgen Ltd is responsible for all aspects of study execution, conduct and reporting.

## 4. Abstract

- Study Title: A Multinational Observational Study to Evaluate the Safety of Repatha® in Pregnancy
- Study Background and Rationale:

Individuals with genetic causes of hypercholesterolaemia comprise a small proportion of the dyslipidaemia population, but suffer a disproportionately high risk of experiencing a cardiovascular event. Approximately 95% of mutations exist within the low density lipoprotein (LDL) receptor and manifest with the clinical diagnosis of familial hypercholesterolaemia (FH) (Rader et al, 2003). Because LDL receptor-mediated endocytosis is the principal mode of hepatic LDL-cholesterol (LDL-C) clearance, compromised LDL receptor function often results in an increase in circulating LDL-C levels. This renders affected individuals extremely vulnerable to the consequences of severe atherosclerotic disease, such as myocardial infarction and stroke: There is a 2-fold excess of coronary heart disease-related deaths relative to age-matched controls in this population (Neil et al, 2008).

A serine protease expressed predominantly in the liver, kidney and intestine (Seidah,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® (evolocumab) is a fully human monoclonal immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with the LDL receptor, thus lowering plasma LDL-C levels.

In Europe, Repatha® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated (Repatha® EPAR, EMA website). **Repatha is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.**

**Additionally, Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.**

Based on modality, mechanism of action, and nonclinical studies, safety issues are not expected with Repatha® use during pregnancy. As a therapeutic monoclonal antibody, placental transfer during organogenesis in humans is expected to be low (DeSesso, 2012; ICH M3 (R2), 2009). Further, the conceptus derives at least 80% of its cholesterol needs from endogenous synthesis rather than from the maternal circulation (Woollett, 2005; Bartels, 2011). 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 (Connor et al, 1978; McMurry et al, 1981; Homanics et al, 1993). Moreover, nonclinical studies have shown that administration of Repatha® to pregnant cynomolgus monkeys throughout gestation (at exposure levels12-times higher than patients receiving Repatha® at 420 mg once monthly (QM)) resulted in no effects on embryo-fetal/neonatal growth and development through to 6 months postpartum (Evolocumab Investigator Brochure 2015). However, clinical data of Repatha® use in pregnancy is limited, therefore safety of Repatha® in pregnancy is considered to be missing information and this is reflected in the Summary of Product Characteristics (SmPC).

The SmPC states the following on use of Repatha® in association with pregnancy:

- There are no or limited amount of data from the use of Repatha® in pregnant women. Animal studies do not indicate direct or indirect effects with respect to reproductive toxicity.
- Repatha® should not be used during pregnancy unless the clinical condition of the woman requires treatment with evolocumab.

**Similarly, s**afety of Repatha® whilst breast-feeding is considered to be missing information. Published literature **indicates that in general, there is** a low risk of maternally-administered monoclonal antibodies resulting in pharmacologically relevant systemic exposures in breastfed infants, the milk-to-serum concentration ratio of IgG being low (Kim et al, 1992; Telemo et al., 1996; Ostensen and Eigenmann, 2004; Mahadevan et al, 2005; Vasiliauskas et al, 2006). In studies of breast-feeding women treated with other therapeutic monoclonal antibodies, these antibodies were not present in breast milk at detectable concentrations (Vasiliauskas et al, 2006, Kane and Acquah, 2009). In addition, large molecules are known to have low oral bioavailability in the infant gastrointestinal tract (Van de Perre, 2003; Lobo et al, 2004; Hurley and Theil, 2011).

The SmPC states the following on use of Repatha® whilst breast-feeding:

- It is unknown whether evolocumab is excreted in human milk.
- A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or discontinue/abstain from Repatha® therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

In light of the limited data available on use of Repatha® in association with pregnancy and/or lactation, this study is being conducted in response to a request by the European Medicines Authority (EMA) to provide data on outcomes of pregnancy in women (and their infants to the age of 12 months) exposed to Repatha® prior to or during pregnancy and/or breast-feeding.

In women of child-bearing age in Europe, South Africa, and Australia those most likely to have been identified as requiring Repatha® for control of hypercholesterolaemia are those diagnosed with FH. Introduction of this particular pharmacological intervention in the majority of non-FH women is anticipated to occur beyond reproductive age.

Considering the low rate of FH diagnosis and therefore the small number of Repatha®-exposed pregnancies anticipated to occur, routine pharmacovigilance surveillance based solely on spontaneous reporting is unlikely to provide the information required by the EMA, in the post-launch period. To address this, a separate study is required, with a targeted, proactive approach to identify potential study subjects and seek appropriate follow-up o**n** outcomes of pregnancy in women with FH who have received Repatha® during pregnancy and/or breast-feeding.

This multinational observational study is expected to enrol female FH patients, identified in collaboration with specialist physicians and patient groups: Females with FH exposed to Repatha® during pregnancy and/or breast-feeding will form the exposed cohort, and females with FH unexposed to Repatha® during pregnancy and breast-feeding will form the internal comparator group. Although no formal comparison of exposed/unexposed subjects is planned, capturing outcomes of pregnancy in a rare population unexposed to Repatha® will provide contemporary reference **data** against which to consider outcomes in exposed pregnancies. **Due to potentially insufficient data and consequent lack of statistical power, it is unlikely that comparisons between the two groups will provide meaningful results, hence, no formal comparison of exposed/unexposed subjects is planned.**

- Research Question and Objectives
  - Primary Objective:

    To describe congenital anomalies in infants of females with FH exposed to Repatha® within 15 weeks prior to or during pregnancy, followed to the age of 12 months.

  - Secondary Objectives:

    - To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to and/or during pregnancy
    - To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to and/or during pregnancy
    - To describe **health and developmental** outcomes in infants up to the age of 12 months, born to females diagnosed with FH and unexposed **or exposed** to Repatha® **during pregnancy and/or breastfeeding.**

- Hypothesis:

  No formal hypothesis will be tested in this study. Statistical analyses will be descriptive only.

- Study Design/Type:

Multinational prospective observational cohort study

- Study Population or Data Resource:

The study population comprises females in Europe, South Africa and Australia diagnosed with FH and who are **either** pregnant or breast-feeding during the study period, and who provide informed consent to participate in the study**, if applicable**

**according to local requirements**. Their infants will also be followed to the age of 12 months**, following consent by the mother (if applicable per local regulations)**.

**(Note: The therapeutic strategy assigned to each patient enrolled in the study will not be specified within this study protocol. Instead, it will be decided according to routine clinical practice, hence the decision for medicinal prescription will be clearly dissociated from the decision to include the patient in the study).**

- Summary of Subject Eligibility Criteria

Inclusion Criteria:

  - Females diagnosed with FH
  - Confirmed pregnancy during the study observation period
    - **Pregnancies identified retrospectively but within the study period will be included**
    - **Multiple pregnancies, occurring in the same woman within the study period, will all be included (as separate pregnancies)**
  - Provided informed consent to follow-up in this study, for subject and their infant(s) born during the study observation period
- Follow-up

Subjects will be followed for outcomes of pregnancy during the study observation period, which for each individual subject will be from 15 weeks prior to pregnancy through to the end of pregnancy (ie, to birth or to loss of the pregnancy). Infants born to subjects during the observation period will be followed from birth to 12 months of age.

The study is anticipated to cover a 10-year period, from June 2016 to June 2026.

- Variables

  **The following types of data/outcomes will be collected:**

  - **Maternal Data:**
    - **Demographics**
    - **Current pregnancy history**
    - **Medical history**
    - **Obstetric history**
    - **Lipid levels**
    - **Medications**

- Congenital anomal**ies**
- Complications of pregnancy
- Outcomes of pregnancy
- Mode of delivery
- Complications of delivery

– **Infant Data:**
  - **Infant status at delivery**
  - **Infant health, growth, and developmental outcomes until 12 months of age**

– Exposure **Data: Exposure** to Repatha® (duration of exposure, doses, dose frequency) within 15 weeks prior to conception and/or during pregnancy and/or whilst breast-feeding

Information available for each subject on all variables will be reported by study site staff in the study-specific sponsor database. The original data source will be patient records, from routine follow-up of subjects. All data will be gathered during routine visits only.

Study Sample Size:

The study will collect data on all pregnancies and births in females diagnosed with FH and identified via the specialist centres/networks, where the patient consents to participate. Based on a conservative estimated FH prevalence of 1 in 500, and a national diagnosis rate varying between 70% and 1% (Nordestgaard 2013), the number of subjects identified for inclusion in this study is not expected to be large. The EMA guideline EMEA/CHMP/203927/2005 “GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING” assumes an overall incidence of birth defects of 3% in order to derive the number of first trimester pregnancies exposed to a medicinal product that is needed to exclude a certain level of risk. The Guideline further states that if no increased incidence of malformations is observed within at least 300 first trimester-exposed, prospectively collected pregnancies with known pregnancy outcomes (births or fetopathological examinations) then the conclusion might be reached that the medicinal product is not responsible for a 10-fold or more increase of the overall incidence of malformations. In accordance with the Guideline, this study will endeavour to enrol 300 pregnancies exposed to Repatha in the first trimester. **The maximum number of unexposed pregnancies will be limited to a ratio of 2 unexposed to 1 exposed; ie, 600 unexposed pregnancies.**

Data Analysis:

Statistical analyses will be descriptive only. No statistical inference or imputations of missing data are planned.

Subject demographics and baseline characteristics will be summarised. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be reported.

## 5. Amendments and Updates

| Amendment/Update | Date Performed |
|---|---|
| **Study Protocol Amendment** | **18 December 2018** |

## 6. Milestones

| Milestone | Planned date |
|---|---|
| Start of data collection | Not before June 2016 (depending on first prescriptions) |
| End of data collection | 10 years after study start. |
| Feasibility report to Competent Authority (CA) | September 2019 |
| Interim reports to CA | Annually according to the international birth date (IBD) |
| Registration in the EU PAS register | Before June 2016 |
| Final report of study results to CA | Mandated within 12 months after end of data collection ie, June 2027 |

## 7. Rationale and Background

### 7.1 Diseases and Therapeutic Area

Individuals with genetic causes of hypercholesterolaemia comprise a small proportion of the dyslipidaemia population, but suffer a disproportionately high risk of experiencing a cardiovascular event. Approximately 95% of mutations exist within the low density lipoprotein (LDL) receptor and manifest with the clinical diagnosis of familial hypercholesterolaemia (FH) (Rader et al, 2003). Because LDL receptor-mediated endocytosis is the principal mode of hepatic LDL-cholesterol (LDL-C) clearance, compromised LDL receptor function often results in an increase in circulating LDL-C levels. This renders affected individuals extremely vulnerable to the consequences of severe atherosclerotic disease, such as myocardial infarction and stroke: There is a

2-fold excess of coronary heart disease-related deaths relative to age-matched controls in this population (Neil et al, 2008).

A serine protease expressed predominantly in the liver, kidney and intestine (Seidah 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 immunoglobulin (Ig) G2 that binds specifically to human PCSK9 and prevents the interaction of PCSK9 with the LDL receptor, thus lowering plasma LDL-C levels.

In Europe, Repatha® is indicated in adults with **established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels**, as an adjunct to correction of other risk factors: in combination with the maximum tolerated dose of a statin with **or without** other lipid-lowering therapies **or, alone or in combination with other lipid-lowering therapies** in patients who are statin-intolerant, or for whom a statin is contraindicated. Repatha is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies (Repatha® EPAR, EMA website). Based on modality, mechanism of action, and nonclinical studies, safety issues are not expected with Repatha® use during pregnancy. As a therapeutic monoclonal antibody, placental transfer during organogenesis in humans is likely to be low (DeSesso, 2012; ICH M3(R2), 2009). Further, the conceptus derives at least 80% of its cholesterol needs from endogenous synthesis rather than from the maternal circulation (Woollett, 2005; Bartels, 2011). 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 (Connor et al, 1978; McMurry et al, 1981; Homanics et al, 1993).

Moreover**,** nonclinical studies have shown that administration of Repatha® to pregnant cynomolgus monkeys throughout gestation (at exposure levels12-times higher than patients receiving Repatha® at 420 mg QM) resulted in no effects on embryo-fetal/neonatal growth and development through to 6 months postpartum (Evolocumab Investigator's Brochure 2015). However, clinical data of Repatha® use in pregnancy is limited, therefore safety of Repatha® in pregnancy is considered to be missing information and this is reflected in the SmPC.

The SmPC states the following on use of Repatha® in association with pregnancy:

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**Similarly, s**afety of Repatha® whilst breast-feeding is considered to be missing information. Published literature **indicates** that **in general,** there is a low risk of maternally-administered monoclonal antibodies resulting in pharmacologically relevant systemic exposures in breastfed infants, the milk-to-serum concentration ratio of IgGs being low (Kim et al, 1992; Telemo et al., 1996; Ostensen and Eigenmann, 2004; Mahadevan et al, 2005; Vasiliauskas et al, 2006). In studies of breast-feeding women treated with other therapeutic monoclonal antibodies, these antibodies were not present in breast milk at detectable concentrations (Vasiliauskas et al, 2006, Kane and Acquah, 2009). In addition, large molecules are known to have low oral bioavailability in the infant gastrointestinal tract (Van de Perre, 2003; Lobo et al, 2004; Hurley and Theil, 2011).

The SmPC states the following on use of Repatha® whilst breast-feeding:

- It is unknown whether evolocumab is excreted in human milk.
- A risk to breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or discontinue/abstain from Repatha® therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

### 7.2 Rationale

In light of the limited data available on use of Repatha® in association with pregnancy and/or lactation, this study is being conducted in response to a request by the EMA to

provide data on outcomes of pregnancy in women (and their infants to the age of 12 months) exposed to Repatha® prior to or during pregnancy and/or breast-feeding.

In women of child-bearing age in Europe, South Africa and Australia those most likely to have been identified as requiring Repatha® for control of hypercholesterolaemia are those diagnosed with FH. Introduction of this particular pharmacological intervention in the majority of non-FH women is anticipated to occur beyond reproductive age.

Considering the low rate of FH diagnosis and the small number of Repatha®-exposed pregnancies anticipated to occur, routine pharmacovigilance surveillance based solely on spontaneous reporting is unlikely to provide the information required by the EMA, in the post-launch period. To address this, a separate study is required, with a targeted, proactive approach to identify cases and seek appropriate follow-up of outcomes of pregnancy in women with FH who have received Repatha® during pregnancy and/or breast-feeding.

This multinational observational study is expected to enrol female FH patients, identified in collaboration with specialist physicians and patient groups:

- Females with FH exposed to Repatha® during pregnancy and/or breast-feeding will form the exposed cohort, and
- Females with FH unexposed to Repatha® during pregnancy and breast-feeding will form the internal comparator group. Although no formal comparison of exposed/unexposed subjects is planned, capturing outcomes of pregnancy in a rare population unexposed to Repatha® will provide contemporary reference **data** against which to consider outcomes in exposed pregnancies.

### 7.3 Statistical Inference (Estimation or Hypothesis)

No formal hypothesis will be tested in this study. Statistical analyses will be descriptive only. No statistical inference is planned.

## 8. Research Question and Objectives

The purpose of the study is to evaluate outcomes of pregnancy in females diagnosed with FH, exposed to Repatha® during pregnancy. This includes follow-up of their infants to the age of 12 months.

### 8.1 Primary Objective

To describe congenital anomalies in infants of females with FH exposed to Repatha® within 15 weeks prior to or during pregnancy, followed to the age of 12 months.

### 8.2 Secondary Objectives

- To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to or during pregnancy
- To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to or during pregnancy
- To describe **health and developmental** outcomes in infants up to the age of 12 months, born to females diagnosed with FH and **unexposed or** exposed to Repatha® **during pregnancy and/or breastfeeding.**

## 9. Research Methods

### 9.1 Study Design

The study is a multinational (Europe, South Africa and Australia) prospective observational cohort study designed to capture data on outcomes of pregnancy in women diagnosed with FH. Within this population, the exposure of interest is administration of Repatha® during pregnancy and/or breast-feeding. The primary and secondary outcome measures are congenital anomaly and other outcomes of pregnancy **or infancy**, respectively.

To maximise the enrolment of eligible subjects this study will be conducted at sites which specialise in treatment of FH patients, and which are connected to local national and regional FH patient groups. All eligible patients at each study site will be invited to consent to be enrolled into the study; there is no limit to the number of subjects enrolled.

At the individual subject level, data of interest include demographics, medical and obstetric history at the time of confirmation of pregnancy within the study observation period. The subject will be followed **to determine** the outcome of pregnancy, including follow-up of the infant(s) to 12 months post-delivery. Data capture may be retrospective if a pregnancy occurring during the study period is detected after delivery.

Study site staff will abstract data from patient notes and entered into the sponsor's electronic database. There will be independent external expert adjudication of congenital anomaly to ensure consistency and accuracy of reporting. Analyses will be conducted by the sponsor.

This is a non-interventional, observational study and is not intended to alter the clinical management of patients.

### 9.2 Setting and Study Population

#### 9.2.1 Study Period

Data will be captured for pregnancies occurring between June 2016 and June 2026.

### 9.2.2 Selection and Number of Sites

Sites in Europe, South Africa and Australia where pregnant FH patients are treated will be considered suitable. These are anticipated to be national or regional FH referral centres, or other specialist sites which treat FH patients. Potential sites will be approached and selection confirmed according to Amgen Standard Operating Procedures (SOPs), based on interest in participation as a study site, willingness and ability to comply with the protocol and data entry conventions, and agreement to follow the subjects throughout the observation period.

**An estimated 50 to** 70 sites are expected to participate in the study. As many countries as possible within Europe, as well as South Africa and Australia, are invited and encouraged to participate. Site identification is expected to continue during the course of the study, to maximise the catchment across the FH population and hence the number of potential study subjects.

To maximise the number of subjects enrolled:

- A key criterion for selection of a study site is that the Investigator is a physician specialising in the treatment of FH.
- The Investigator will be aware of pregnancies in the regional or national FH population and will routinely advise women on management of their FH during pregnancy and breast-feeding.
- The Investigator and the sponsor will seek to proactively engage with national and local FH patient networks, to raise awareness of the study.
- Physicians may also be contacted if Repatha®-exposed pregnancies at their clinic are reported through Amgen's routine surveillance system; patient confidentiality will not be breached; the physician will be alerted to the pregnancy and will be encouraged to consider the patient's eligibility and invite them to consent to enrol in the study.
- There is no limit on the number of sites to be opened; as many sites as possible will be sought, in all participating countries, with no minimum on the number of eligible subjects expected to be enrolled at any site.

### 9.2.3 Subject Eligibility

#### 9.2.3.1 Inclusion Criteria

- Females diagnosed with FH
- Confirmed pregnancy during the study observation period
  - **Pregnancies identified retrospectively but within the study period will be included**
  - **Multiple pregnancies, occurring in the same woman within the study period, will all be included (as separate pregnancies)**
- Provided informed consent to follow-up in this study, for subject and their infant(s) born during the study observation period

#### 9.2.3.2 Exclusion Criteria

There are no exclusion criteria

### 9.2.4 Matching

Not applicable

### 9.2.5 Baseline Period

The index date is the date of diagnosis of pregnancy. The baseline period covers subject history prior to the index date. Demographic factors and all relevant medical and clinical history at diagnosis of pregnancy will be reported as baseline subject status.

### 9.2.6 Study Follow-up

Follow-up duration may differ for each individual subject, depending on the outcome of pregnancy: Initial baseline information will be recorded at confirmation of pregnancy and the subject will be followed for outcome of pregnancy **and, if breastfeeding following a live birth, until termination of breastfeeding**. Information on pregnancy outcome, and on infant health **and development up to** 12 months after delivery, will be captured.

## 9.3 Outcomes - Variables

**Information available for each subject on all variables will be reported by study site staff in the study-specific database held by the sponsor. The original data source will be patient (maternal – infant) records, from routine follow-up of subjects:**

- **Maternal Data:**
  - **Demographics:**
    - **Country of residence**
    - **Age (at start of pregnancy, categorized into ≤ 19, 20-24, 25-29, 30-34, 35-39, 40-44, ≥ 45 year age categories)**
    - **Education (highest level)**
    - **Occupation**
    - **Height and weight (to calculate body mass index, categorised into < 20, 20-24, 25-29, ≥ 30 kg/m$^2$ body mass index categories)**
  - **Current pregnancy history:**
    - **Date of last menstrual period**
    - **Estimated date of delivery**
    - **Number of fetuses**
    - **Treatment for infertility**

- **Medical history:**
  - **FH diagnosis status and method of diagnosis**
  - **Presence of significant comorbid conditions (hypertension, diabetes mellitus, epilepsy, other)**
  - **Family history of congenital disorders**
- **Obstetric history:**
  - **Number of previous pregnancies and outcome**
  - **Previous maternal pregnancy complications**
  - **Previous fetal/neonatal abnormalities**
  - **History of subfertility**
- **Medications (product, dose, dose dates) taken within 3 months prior to or during pregnancy (excluding medication routinely administered during labour/delivery) and/or breast-feeding**
- **Lipid levels (triglycerides, total cholesterol, LDL-C, HDL-C)**
- **Congenital anomaly including congenital abnormality or malformation as defined by European Surveillance of Congenital Anomalies (EUROCAT) (See Appendix E for full list)**
- **Complications of pregnancy:**
  - **Pre-eclampsia**
  - **Gestational diabetes**
- **Outcomes of pregnancy: (See Appendix F for further definition):**
  - **Live birth (with / without congenital anomaly)**
  - **Neonatal death (with / without congenital anomaly)**
  - **Stillbirth (with / without congenital anomaly)**
  - **Elective termination (with / without congenital anomaly)**
  - **Miscarriage (with / without congenital anomaly)**
  - **Spontaneous abortion**
  - **Ectopic pregnancy**
  - **Molar pregnancy**
- **Mode of delivery:**
  - **Normal vaginal delivery**
  - **Operative vaginal delivery**
  - **Vaginal breech delivery**
  - **Caesarean section**
- **Complications of delivery:**
  - **Abnormal Cord gas**
  - **Fetal heart rate abnormalities**
  - **Abnormal amniotic fluid**

- **Blood transfusion resulting from post-partum haemorrhage;**
- **Thromboembolism**

- **Infant Data:**
  - **Infant status at delivery:**
    - **Infant(s) sex**
    - **Gestational age**
    - **Birth weight**
    - **Apgar score**
  - **Infant outcomes until 12 months of age:**
    - **Weight growth**
    - **Developmental delay (not meeting the usual developmental milestones during the first 12 months of age)**
    - **Hospitalisations (total number of days hospitalised; number of hospitalisation episodes during the first 12 months)**
    - **Chronic medication (defined as medication prescribed for a period of 4 weeks or more)**
    - **Breastfeeding (date of start/stop, exclusive breastfeeding [Yes/No])**

- Exposure Variables:
  - Exposure to Repatha® (duration of exposure, doses, dose dates) within 15 weeks prior to conception and/or during pregnancy and/or whilst breast-feeding. In adult subjects a single dose of Repatha® constitutes exposure. In infants, exposure may occur in utero and/or via breast milk, within 15 weeks following the date of Repatha® dosing in the mother.

### 9.3.1 Exposure Assessment

Exposure to Repatha® in the 15 weeks (ie, 5 half-lives of Repatha®) prior to or during pregnancy or breast-feeding will be entered by site staff into study-specific electronic case report forms and will be reported descriptively by dose and dates of administration. Exposure will be counted in doses of Repatha®.

**The study population comprises females in Europe, South Africa and Australia diagnosed with FH and who are either pregnant or breast-feeding during the study period, and who provide informed consent to participate in the study, if applicable according to local requirements. Their infants will also be followed to the age of 12 months, following consent by the mother (if applicable per local regulations).**

**(Note: The therapeutic strategy assigned to each patient enrolled in the study will not be specified within this study protocol. Instead, it will be decided according to**

**routine clinical practice, hence the decision for medicinal prescription will be clearly dissociated from the decision to include the patient in the study).**

### 9.3.2 Outcome Assessment

Outcome Measures:

- The primary outcome measure is congenital anomaly. Any incidence of congenital anomaly will be diagnosed and classified by the study site Investigator, or by the subject's treating physician (eg, an obstetrician, paediatrician, neonatologist) if this is not the Investigator, and reported on the study-specific eCRF. Supporting documentation will be requested to enable independent adjudication of the diagnosis, by an external expert not participating as a study investigator. Where supporting documentation is not held at the same clinic/hospital/institution as the study site, contracts will be executed to allow sharing of medical records, as necessary.
- Secondary outcome measures include:
    - Pregnancy outcomes (live birth(s), stillbirth, spontaneous loss, elective termination, ectopic pregnancy, complications of pregnancy (eg, pre-eclampsia, gestational diabetes)
    - Delivery outcomes (mode of delivery; complications including requirement for blood transfusion, thromboembolism, fetal distress, amniotic fluid abnormality)
    - Infant status at delivery: gender; gestational age; Apgar score; birth weight
    - Infant outcomes at 6 and 12 months post-delivery (including growth, hospitalisation, chronic medication)

The secondary outcome measures will be reported on the study-specific eCRF, from information entered into the subject's notes as part of routine follow-up. Where supporting documentation is not held at the same clinic/hospital/institution as the study site, contracts will be executed to allow sharing of medical records, as necessary.

Adverse outcomes requiring a clinical diagnosis of congenital anomaly will be subject to the same independent adjudication as the primary outcome.

### 9.3.3 Covariate Assessment

Not applicable

### 9.3.4 Validity and Reliability

Study variables stated in this protocol are objective, relevant to the question under study and are accepted as appropriate by regulatory authorities.

Reports of clinically significant outcomes will receive medical review.

Independent expert adjudication will be sought for any reports of congenital anomaly.

Reporting of exposure is expected to be accurate; subjects with a genetic condition (FH) are likely to be aware of treatments taken for that condition, especially around pregnancy and breast-feeding. The burden of reporting dosing dates is not excessive, as Repatha® is administered regularly, once every two weeks or once monthly.

### 9.4 Data Sources

Data will be provided by study site staff, utilising subject medical notes to abstract information in order to complete electronic CRFs in the study-specific electronic database, which will be provided by the sponsor.

Medical notes will be patient records at the study site and are also expected to include records from maternity/obstetric units.

### 9.5 Study Size

The study will collect data on all pregnancies and births in females diagnosed with FH and identified via the specialist centres/networks, where the patient consents to participate. Based on a conservative estimated FH prevalence of 1 in 500, and a national diagnosis rate varying between 70% and 1% (Nordestgaard 2013), the number of subjects identified for inclusion in this study is not expected to be large. The EMA guideline EMEA/CHMP/203927/2005 “GUIDELINE ON RISK ASSESSMENT OF MEDICINAL PRODUCTS ON HUMAN REPRODUCTION AND LACTATION: FROM DATA TO LABELLING” assumes an overall incidence of birth defects of 3% in order to derive the number of first trimester pregnancies exposed to a medicinal product that is needed to exclude a certain level of risk. The Guideline further states that if no increased incidence of malformations is observed within at least 300 first trimester-exposed, prospectively collected pregnancies with known pregnancy outcomes (births or fetopathological examinations) then the conclusion might be reached that the medicinal product is not responsible for a 10-fold or more increase of the overall incidence of malformations. In accordance with the Guideline, this study will endeavour to enrol 300 pregnancies exposed to Repatha in the first trimester **in order to meet the primary objective of this study. The maximum number of unexposed pregnancies will be limited to a ratio of 2 unexposed to 1 exposed; ie, the maximum will be 600 unexposed pregnancies. In addition, the maximum of unexposed pregnancies originating from a single country will be limited to the minimum of N = 150 or tenfold the expected proportion of births out of the combined total of live births as reported by the relevant Bureaus of Statistics in the participating countries (Appendix H). For example, the observed number of live births in Norway in 2017**

**represented 1.5% of the births across all participating countries. Therefore, no more than N = 88 (10 x 1.5% = 15% of 600) unexposed pregnancies will originate from Norway. The observed number of United Kingdom births represents 19.6% of all 2017 live births across all countries; tenfold 19.6% of 600 would exceed the target of 600, therefore the number of unexposed pregnancies from the United Kingdom will be capped at N=150. This will ensure we enrol as many unexposed pregnancies as possible whilst avoiding that unexposed pregnancies will originate from a single country only.**

### 9.6 Data Management

Data are abstracted by site staff from subject notes into an electronic database provided by the sponsor. The sponsor provides protocol-specific training to all site staff delegated to abstract subject data. An eCRF Completion Guideline is provided.

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, CRFs and other pertinent data) provided that subject confidentiality is respected.

The Clinical Monitor or designee is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of research. The Clinical Monitor, or designee is to have access to subject medical records and other study-related records needed to verify the entries on the CRFs in accordance with the local laws and regulations.

The Investigator agrees to cooperate with the Clinical Monitor, or designee to ensure that any problems detected in the course of these monitoring visits, including delays in completing CRFs, are resolved.

In accordance with the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the electronic CRFs must be maintained and available upon request.
- Updates to electronic CRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data is checked for consistency, omissions, and any apparent discrepancies. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.
- The Investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that the Investigator inspected or reviewed the data on the CRF, the data queries, and site notifications, and agrees with the content.

### 9.6.1 Obtaining Data Files

Not applicable

### 9.6.2 Linking Data Files

Not applicable

### 9.6.3 Review and Verification of Data Quality

Automatic edit checks within the database and further manual review by the sponsor help to ensure quality and completeness of the data. Data queries are sent to site for clarification and resolution of discrepancies.

## 9.7 Data Analysis

### 9.7.1 Planned Analyses

#### 9.7.1.1 Interim Analyses

**T**he appropriate regulatory authorities will receive:

- Interim reports of all analyses performed, to be submitted annually. (See Appendix G for **an example** Summary Table **template** to be included in the report)
- A feasibility report three years after study commencement, summarising the number of subjects enrolled, any exposure to Repatha® and describing primary and secondary outcome data.

#### 9.7.1.2 Primary Analysis

The primary analysis will be conducted at the end of the study observation period, which is currently scheduled to occur ten years after study commencement.

### 9.7.2 Planned Method of Analysis

#### 9.7.2.1 General Considerations

Statistical analyses will be descriptive only. No statistical inference or imputations of missing data are planned.

Subject demographics and baseline characteristics will be summarised. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, minimum, and maximum. For categorical variables, the frequency and percentage will be reported.

Collection of study data may be both retrospective and/or prospective, depending on the time of enrolment of each study subject during the study observation period. Data obtained from retrospective and prospective subject identification will be reported separately.

**Multiple pregnancies, occurring in the same woman within the study period, will be reported as separate pregnancies (with an addition of a relevant footnote in the respective tables, indicating that two or more pregnancies occurred in the same woman).**

#### 9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

For all study-related parameters, data are recorded as part of pregnancy follow-up in this cardiovascular high-risk population, and a high degree of completeness of follow-up and data recording can be expected. **However, the necessity of obtaining data from multiple sources may incur an increased risk of being unable to obtain specific sets of patient notes.** Proactive follow-up will also be encouraged.

There will be no imputation **of** missing data.

#### 9.7.2.3 Descriptive Analysis

##### 9.7.2.3.1 Description of Study Enrolment

All eligible patients identified at each study site will be invited by the Investigators to provide informed consent to be enrolled into the study.

##### 9.7.2.3.2 Description of Subject Characteristics

Subjects are women diagnosed with FH, treated at centres in Europe, South Africa and Australia, with pregnancy confirmed during the study observation period and who provide informed consent to participate in the study.

Exposed subjects are women who received Repatha® during pregnancy and/or breast-feeding; unexposed subjects are women who have not received Repatha® during pregnancy and/or breast-feeding. In infants, exposure may occur in utero and/or via breast milk, within 15 weeks following the date of Repatha® dosing in the mother.

#### 9.7.2.4 Analysis of the Primary and Secondary Endpoints

Analysis of Primary Objective:

Congenital anomalies will be summarised and descriptive statistics will be presented.

Congenital anomalies will be defined according to ICD10-BPA codes **(codes included in Appendix E: EUROCAT Subgroups of Congenital Anomalies)**.

Analyses of Secondary Objectives:

Secondary objective outcome measures will be summarised and descriptive statistics will be presented.

**Due to potentially insufficient data and consequent lack of statistical power, it is unlikely that comparisons between the 2 groups will provide meaningful results, hence, no formal comparison of exposed/unexposed subjects is planned.**

#### 9.7.2.5 Sensitivity Analysis

None planned

#### 9.7.2.6 Subgroup Analysis

None planned

#### 9.7.2.7 Stratified Analysis

**For the secondary objective of describing health and developmental outcomes in infants up to 12 months of age, a**nalyses will be stratified according to **whether the infant was** expos**ed** to Repatha® (in the 15 weeks prior to conception or in the first trimester of pregnancy, in the second or third trimester of pregnancy, and/or whilst breast-feeding)**. In addition, a stratified analysis will be conducted** by exposure to other lipid modifying therapies (including statins, PCSK9 inhibitors, CETP inhibitors, and others).

**In addition, data obtained from retrospective and prospective subject identification will be reported separately (to account for the possibility that subjects enrolled retrospectively may differ from those enrolled prospectively).**

**Results from mothers are to be presented using the following columns: (i) 'unexposed', (ii) 'exposed but stopped prior to conception', (iii) 'exposure in 1st trimester (up to 15 weeks)', (iv) 'exposure in 2nd/3rd trimesters', (v) 'exposed at conception and during 1st trimester but stopped during 2nd/3rd trimesters, (vi) 'exposed throughout pregnancy', (vii) 'exposure during breastfeeding only', and (viii) 'exposure anytime during pregnancy and up to 15 weeks, and breastfeeding'. Columns will not be mutually exclusive.**

#### 9.7.2.7.1 Sensitivity Analysis for Residual Confounding and Bias

Not applicable

#### 9.7.2.7.2 Other Sensitivity Analysis

None planned

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

Apart from the primary and secondary analyses, no other Safety analyses are planned as part of this study.

## 9.8 Quality Control

Source data verification will be performed at the study site, in accordance with Amgen SOPs.

The Investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on CRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's CRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements to include:

- Subject files containing completed CRF, informed consent forms, as applicable, and subject identification list
- Study files containing the protocol with all amendments, copies of pre-study documentation, and all correspondence to and from the IRB/IEC or other relevant ethical review board and Amgen

In addition, all original source documents supporting entries in the CRFs must be maintained and be readily available.

Retention of study documents will be governed by the contractual agreement with Amgen.

Amgen retains all data, programs and outputs generated for the study. At study close, data are uploaded from the Medidata Rave database and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard statistical programming processes will be followed.

## 9.9 Limitations of the Research Methods

### 9.9.1 Information Bias

Information bias **may occur from participants who are recruited retrospectively more likely to have adverse outcomes. This will occur because participants with adverse outcomes will make the clinician consider recruiting them.**

### 9.9.2 Selection Bias

The intention is to enrol as many eligible subjects as possible, with no limit on numbers at site or country level. The inclusion criteria are not restrictive, and all eligible FH women identified will be invited to enrol into the study.

**Selection bias may occur due to pregnant women without adverse outcomes potentially being less likely to be told about the study, or less inclined to participate in the study.** To help to minimi**s**e selection bias arising from preferential enrolment of subjects experiencing adverse outcomes rather than those with normal outcomes, sites will be requested to enrol all eligible patients whether retrospectively or prospectively identified, and regardless of outcomes which are already known.

To account for the possibility that subjects enrolled retrospectively may differ from those enrolled prospectively, data obtained from retrospective and prospective subject identification will be reported separately.

Study sites will be asked to record, annually for the duration of the study, the number of pregnant FH women attending their clinic, and the number who are eligible but do not consent to enrol into the study. Comparing these numbers with the number of enrolled subjects will help to assess case ascertainment.

### 9.9.3 Limitations due to Missing Data and/or Incomplete Data

**Although the necessity of obtaining data from multiple sources may incur an increased risk of being unable to obtain specific sets of patient notes, m**issing/incomplete data is unlikely to be a limitation for subjects identified and enrolled into this study, as physicians treating FH women pay particular attention to their clinical management during pregnancy and breast-feeding. It is not expected that information on outcomes will be missing, due to the critical nature of follow-up of pregnant women and their infants regardless of an adverse or a normal outcome. Additionally, Amgen will review all study data thoroughly and will follow up directly with study sites to query for missing information.

## 9.10 Other Aspects

The sites chosen to participate in this study are regional or national referral centres, with links to other FH specialists; in collaboration with these sites, and with FH patient networks and associations, Amgen will raise and proactively maintain awareness of the study to maximize the number of cases detected.

# 10. Protection of Human Subjects

## 10.1 Informed Consent

An initial sample informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site**, according to local regulations**. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Before a subject's participation in the study, the Investigator is responsible for obtaining written informed consent, where applicable by local regulations, from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific activities/assessments are conducted. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject/patient, to the subject's/patient's participation in the study.

The acquisition of informed consent and the subject's/patient's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the Investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

In addition to the above, each study site must follow all locally applicable regulations and requirements for obtaining parental/legally acceptable representative consent for follow-up of infants born to study subjects.

### 10.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

A copy of the protocol, proposed informed consent form, as applicable, other written subject/patient information, and any proposed advertising material must be submitted to the IRB/IEC or other relevant ethical review board for written approval. A copy of the written approval of the protocol, and informed consent form, as applicable must be received by Amgen before the study can be executed.

The Investigator must submit and, where necessary, obtain approval from the IRB/IEC or other relevant ethical review board for all subsequent protocol amendments and changes to the informed consent document, as applicable. The Investigator is to notify the IRB/IEC or other relevant ethical review board of deviations from the protocol or serious adverse event(s) occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The Investigator is responsible for obtaining annual IRB/IEC or other relevant ethical review board approval /renewal throughout the duration of the study. Copies of the Investigator's reports, where applicable by local regulations and the IRB/IEC or other relevant ethical review board continuance of approval must be sent to Amgen.

### 10.3 Subject Confidentiality

The Investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the CRFs demographics page, in addition to the unique subject identification number, include the age at time of enrolment.
- Documents that are not for submission to Amgen (eg, signed informed consent forms, as applicable) are to be kept in confidence by the Investigator, except as described below.

In compliance with Local country regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB/IEC or other relevant ethical review board direct access to review the subject's original medical records for verification of study-related activities and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the subject to permit such individuals to have access to his/her study-related records, including personal information.

## 11. Collection of Safety Information and Product Complaints

In this study, Safety reporting is required only for subjects exposed to Repatha®

For subjects known to be exposed to Repatha® within the 15 weeks prior to or during pregnancy and/or during breastfeeding, a Pregnancy Notification Worksheet and/or Lactation Notification Worksheet (Appendix I), as appropriate, is to be submitted to Amgen **and will be collected until termination of breastfeeding, otherwise until 12 months post-partum**.

### 11.1 Definition of Safety Events

#### 11.1.1 Adverse Events

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

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated

with the use of a medicinal product(s), combination product or medical device whether or not considered related to the product(s). The definition of an adverse event includes:

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

It is the investigator's responsibility to evaluate whether an adverse event is related to an Amgen product prior to reporting the adverse event to Amgen. Regardless of causality, for this study all adverse events (non-serious, serious, related and non-related) experienced by subjects exposed to Repatha® should be reported to Amgen.

An adverse device effect is any adverse event related to the use of a medical device. Adverse device effects include adverse events resulting from insufficient or inadequate instructions for use, adverse events resulting from any malfunction of the device, or adverse events resulting from use error or from intentional misuse of the device.

### 11.1.2 Serious Adverse Events

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

- is fatal
- is life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an "other significant medical hazard" that does not meet any of the above criteria

A hospitalization meeting the regulatory definition for "serious" is any in-patient hospital admission that includes a minimum of an overnight stay in a healthcare facility.

"Other significant medical hazards" refer to important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, and blood dyscrasias, drug-induced liver injury, events that necessitate an emergency room visit, outpatient surgery, or other events that require other urgent intervention.

### 11.1.3 Other Safety Findings

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

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

### 11.1.4 Product Complaints

Product Complaints include any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of a product or device after it is released for distribution to market or clinic by either Amgen or by distributors and partners for whom Amgen manufactures the material. This includes any drug(s) or device(s) provisioned and/or repackaged /modified by Amgen. Drug(s) or device(s) includes investigational product.

## 11.2 Safety Reporting Requirements

The Investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the Investigator or reported by the subject that occur during the **study** observation period are recorded in the subject's appropriate study documentation. **The observation period for this study consists of 2 distinct periods: 1) the retrospective observation period that is defined as the time between diagnosis of pregnancy and the subject's enrolment into the study and, 2) the prospective observation period defined as the time between subject's enrolment date until the end of her and the infant's follow-up.**

**For safety events that occurred in the retrospective observation period, the date on which the investigator accessed the subject's medical charts to abstract the relevant retrospective information should be entered into the field "Date Investigator became aware of this Event" on the Event eCRF.** Safety events **identified in both the retrospective and prospective period** must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness.
**Non-serious adverse events must be reported in an expeditious manner, not to exceed 15 calendars days of investigator awareness.**

If the electronic data capture (EDC) system is unavailable to the site staff to report the adverse event, the information is to be reported to Amgen via a paper Electronic Adverse Event Contingency Report Form within 1 business day of the Investigator's awareness. For EDC studies where the first notification of an Adverse Event is reported to Amgen via the Electronic Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

See Appendix C for sample Electronic Adverse Event Contingency Report Form, Appendix D for Additional Safety Reporting Information regarding the adverse event grading scale used in this study.

The Investigator may be asked to provide additional information for any event submitted, which may include a discharge summary or extracts from the medical record. Information provided about the event must be consistent with information recorded on study Case Report Forms (CRFs) where safety data may also be recorded (eg, Event CRF).

#### 11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required to regulatory authorities, Investigators/institutions, IRBs/IECs or other relevant ethical review board(s) in accordance with Pharmacovigilance guidelines and in compliance with local regulations. The Investigator is to notify the appropriate IRB/IEC or other relevant ethical review board of Serious Adverse Events in accordance with local procedures and statutes.

Adverse reactions that are suspected to be related to medicinal products other than Repatha® should be notified by the Investigator to the competent authority in the Member State where the reactions occurred or to the marketing authorisation holder of the suspected medicinal product in accordance with local reporting requirements.

## 12. Administrative and Legal Obligations

### 12.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IRB/IEC or other relevant ethical review board must be informed of all amendments and give approval. The Investigator must send a copy of the approval letter from the IRB/IEC or other relevant ethical review board to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study

according to the contractual agreement. The Investigator is to notify the IRB/IEC or other relevant ethical review board in writing of the study's completion or early termination and send a copy of the notification to Amgen.

## 13. Plans for Disseminating and Communicating Study Results

The intent is to publish the results from this study. Publication may be in the form of Congress abstracts or posters, and/or manuscript(s).

### 13.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

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Evolocumab Investigator's Brochure, Edition 9, September 2015

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# 15. Appendices

## Appendix A. List of Stand-alone Documents

None

## Appendix B. ENCePP Checklist for Study Protocols

**Study title:**
A Multinational Observational Study to Evaluate the Safety of Repatha® in Pregnancy

**Study reference number:**
20150162

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | Sctn 6 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | Sctn 6 |
| 1.1.3 Study progress report(s) | ☒ | ☐ | ☐ | Sctn 6 |
| 1.1.4 Interim progress report(s) | ☒ | ☐ | ☐ | Sctn 6 |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | Sctn 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | Sctn 6 |

Comments:

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

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | | | | |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | Sctn 7.2 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | Sctn 8.1/2 |
| 2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | Sctn 8 |
| 2.1.4 Which formal hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:
This is a descriptive study with no formal hypothesis

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design) | ☒ | ☐ | ☐ | Sctn 9.1 |
| 3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated? | ☒ | ☐ | ☐ | Sctn 9.2.2 |
| 3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☐ | ☐ | ☒ | |

Comments:
The number of exposed cases is expected to be very small; analyses are descriptive only

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | Sctn 9.1.2 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period? | ☒ | ☐ | ☐ | Sctn 9.1.1 |
| 4.2.2 Age and sex? | ☒ | ☐ | ☐ | Sctn 9.1.3 |
| 4.2.3 Country of origin? | ☒ | ☐ | ☐ | Sctn 9.1.2 |
| 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | Sctn 9.1.3 |
| 4.2.5 Co-morbidity? | ☐ | ☐ | ☒ | |
| 4.2.6 Seasonality? | ☐ | ☐ | ☒ | |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | Sctn 9.1 |

Comments:

There are no co-morbidities or seasonality under study

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure) | ☒ | ☐ | ☐ | Sctn 9.2.1 |
| 5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study) | ☒ | ☐ | ☐ | Sctn 9.2.4 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☒ | ☐ | ☐ | Sctn 9.6.3 |
| 5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☒ | ☐ | ☐ | Sctn 9.2.1 |
| 5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured? | ☒ | ☐ | ☐ | Sctn 9.2.1 |

Comments:

Exposure is classified as beginning at 15 weeks prior to conception (5 halflives of Repatha), and a single dose of Repatha at any time during pregnancy or breastfeeding is classified as exposure

| **Section 6: Endpoint definition and measurement** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 6.1 Does the protocol describe how the endpoints are defined and measured? | ☒ | ☐ | ☐ | Sctn 9.2.2 |
| 6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | Sctn 9.2.2 |

Comments:

Endpoints will be reported verbatim, coded in ICD10-BPA according to Eurocat classification and independently adjudicated where congenital anomaly is the outcome

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

Comments:

Confounding is not applicable for this study

| **Section 8: Data sources** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.) | ☒ | ☐ | ☐ | 9.6.2 |
| 8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.) | ☒ | ☐ | ☐ | 9.6.2 |
| 8.1.3 Covariates? | ☒ | ☐ | ☐ | 9.6.2 |
| 8.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | Sctn 9.1/6 |
| 8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | Sctn 9.1/6 |
| 8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.) | ☒ | ☐ | ☐ | Sctn 9.2 |
| 8.3 Is a coding system described for: | | | | |
| 8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10) | ☒ | ☐ | ☐ | Appendix C |
| 8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events) | ☒ | ☐ | ☐ | Appendix C |
| 8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC)Classification System) | ☐ | ☐ | ☒ | |
| 8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☐ | ☒ | |

Comments:

Exposure coding is not applicable as Repatha (band name) is the only exposure.
Baseline covariates and exposure to concomitant medications other than Repatha throughout the observation period will be reported descriptively; it is not anticipated that analyses by covariate subgroups will be performed.
No linkage will be performed.

| **Section 9: Study size and power** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 9.1 Is sample size and/or statistical power calculated? | ☐ | ☐ | ☒ | |

Comments:

This is a signal detection study and is not powered for statistical significance

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 10.1 Does the plan include measurement of excess risks? | ☐ | ☐ | ☒ | |
| 10.2 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | Sctn 9.6.2 |
| 10.3 Are descriptive analyses included? | ☒ | ☐ | ☐ | Sctn 9.6.2 |
| 10.4 Are stratified analyses included? | ☒ | ☐ | ☐ | Sctn 9.6.3 |
| 10.5 Does the plan describe methods for adjusting for confounding? | ☐ | ☐ | ☒ | |
| 10.6 Does the plan describe methods addressing effect modification? | ☐ | ☐ | ☒ | |

Comments:

Descriptive analyses only; confounding is not applicable

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 11.1 Is information provided on the management of missing data? | ☒ | ☐ | ☐ | Sctn 9.8.2 |
| 11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | Sctn 9.7 |
| 11.3 Are methods of quality assurance described? | ☒ | ☐ | ☐ | Sctn 9.5 |
| 11.4 Does the protocol describe possible quality issues related to the data source(s)? | ☒ | ☐ | ☐ | Sctn 9.7 |
| 11.5 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | Sctn 9.2.4 |

Comments:

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss: | | | | |
| 12.1.1 Selection biases? | ☒ | ☐ | ☐ | Sctn 9.8.1 |
| 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☒ | ☐ | ☐ | Sctn 9.8.1 |
| 12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | Sctn 9.6.1 |
| 12.3 Does the protocol address other limitations? | ☒ | ☐ | ☐ | Sctn 9.8.2 |

Comments:

A report on study feasibility is planned at 3 years post-initiation.

| **Section 13: Ethical issues** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described? | ☒ | ☐ | ☐ | Sctn10.1/2 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☒ | ☐ | ☐ | Sctn 10.3 |

Comments:

No ethical review has yet taken place

| **Section 14: Amendments and deviations** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document future amendments and deviations? | ☒ | ☐ | ☐ | Sctn 5 |

Comments:

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Page Number(s)** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | Sctn 9.6.1 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | Sctn 13 |

Comments:

Name of the main author of the protocol: PPD [redacted]

Date: 9/11/2015

Signature: PPD [redacted]

## Appendix C. Sample Electronic Adverse Event Contingency Report Form

AMGEN
Study # 20150162
Repatha® (evolocumab)

**Electronic Adverse Event Contingency Report Form**
**For Restricted Use**

**Reason for reporting this event via fax**
**The Clinical Trial Database (eg. Rave):**

☐ Is not available due to internet outage at my site
☐ Is not yet available for this study
☐ Has been closed for this study

***<<For completion by COM/Study manager/Author prior to providing to sites: SELECT OR TYPE IN A FAX#>>***

**1. SITE INFORMATION**

| Site Number | Investigator | Country |
|---|---|---|
| | | |

| Reporter | Phone Number | Fax Number |
|---|---|---|
| | ( ) | ( ) |

**2. SUBJECT INFORMATION**

| Subject ID Number | Age at event onset | Sex | Race | If applicable, provide End of Study date |
|---|---|---|---|---|
| | | ☐F ☐M | | |

**If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____**
**and start date:** Day ____ Month ____ Year ____

**3. ADVERSE EVENT**

**Provide the date the Investigator became aware of this information: Day____ Month____ Year____**

| Adverse Event **diagnosis** or syndrome<br>**If diagnosis is unknown, enter signs / symptoms and provide diagnosis, when known, in a follow-up report**<br>*List one event per line. If event is fatal, enter the cause of eeath. Entry of "death" is not acceptable, as this is an outcome.* | Date Started<br>Day Month Year | Date Ended<br>Day Month Year | Check only if event occurred before first dose of drug under study | Is event serious? | If serious enter Serious Criteria code *(see codes below)* | Relationship<br>Is there a reasonable possibility that the Event may have been caused by Amgen drug under study or an Amgen device used to administer the Amgen drug under study? | | | | | | | | Outcome of Event<br>-Resolved<br>-Not resolved<br>-Fatal<br>-Unknown | Check only if event is related to study procedure<br>eg, biopsy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Repatha® evolocumab | | Prefilled Syringe | | Prefilled Autoinjector | | Automated Mini-Doser | | | |
| | | | | | | No✓ | Yes✓ | No✓ | Yes✓ | No✓ | Yes✓ | No✓ | Yes✓ | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |
| | | | | ☐Yes ☐No | | | | | | | | | | | |

**Serious Criteria:** **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

**4. Was subject hospitalized or was a hospitalization prolonged due this event?** ☐No ☐Yes If yes, please complete all of Section 4

| Date Admitted<br>Day Month Year | Date Discharged<br>Day Month Year |
|---|---|
| | |

| AMGEN<br>Study # 20150162<br>Repatha® (evolocumab) | Electronic Adverse Event Contingency Report Form<br>For Restricted Use |
|---|---|

| Site Number | Subject ID Number |
|---|---|
| | |

**9. OTHER RELEVANT TESTS *(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes If yes, please complete:

| Date (Day Month Year) | Additional Tests | Results | Units |
|---|---|---|---|
| | | | |
| | | | |
| | | | |
| | | | |

**10. CASE DESCRIPTION *(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

| Signature of Investigator or Designee _ | Title | Date |
|---|---|---|
| _____<br>*I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.* | | |

## Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

| Grade | Amgen Standard Adverse Event Severity Scoring System |
|---|---|
| 1 | MILD: Aware of sign or symptom, but easily tolerated |
| 2 | MODERATE: Discomfort enough to cause interference with usual activity |
| 3 | SEVERE: Incapacitating with inability to work or do usual activity |

## Appendix E. EUROCAT Subgroups of Congenital Anomalies

| EUROCAT Subgroups | ICD10-BPA | ICD9-BPA | Comments | Excluded minor anomalies post-2005 | Excluded minor anomalies pre-2005 | Subgroup binary variable number (al) |
|---|---|---|---|---|---|---|
| All anomalies * | Q-chapter, D215, D821, D1810^, P350, P351, P371 | 74, 75, 27910, 2281^, 76076, 76280, 7710, 7711, 77121 | | Exclude all minor anomalies as specified in Guide 1.4, section 3.2 | Exclude all minor anomalies as specified in Guide 1.2 (ICD9 and ICD10) | al1 |
| Nervous system | Q00, Q01, Q02, Q03, Q04, Q05, Q06, Q07 | 740, 741, 742 | | Q0461, Q0782 | | al2 |
| Neural Tube Defects | Q00, Q01, Q05 | 740, 741, 7420 | | | | al3 |
| Anencephalus and similar | Q00 | 740 | | | | al4 |
| Encephalocele | Q01 | 7420 | Exclude if associated with anencephalus subgroup | | | al5 |
| Spina Bifida | Q05 | 741 | Exclude if associated with anencephalus or encephalocele subgroups | | | al6 |
| Hydrocephalus | Q03 | 7423 | Exclude hydranencephaly 74232. Exclude association with NTD subgroup | | | al7 |
| Microcephaly | Q02 | 7421 | Exclude association with NTD subgroup | | | al8 |
| Arhinencephaly / holoprosencephaly | Q041, Q042 | 74226 | | | | al9 |
| Eye | Q10-Q15 | 743 | | Q101-Q103, Q105, Q135 | 74365 | al10 |
| Anophthalmos / microphthalmos | Q110, Q111, Q112 | 7430, 7431 | | | | al11 |
| Anophthalmos | Q110, Q111 | 7430 | | | | al12 |
| Congenital cataract | Q120 | 74332 | | | | al13 |
| Congenital glaucoma | Q150 | 74320 | | | | al14 |
| Ear, face and neck | Q16, Q17, Q18 | 744 | | Q170-Q175, Q179, Q180-Q182, Q184-Q187, Q1880, Q189 | 74411, 74412, 7443, 74491 | al15 |
| Anotia | Q160 | 74401 | | | | al16 |

| EUROCAT Subgroups | ICD10-BPA | ICD9-BPA | Comments | Excluded minor anomalies post-2005 | Excluded minor anomalies pre-2005 | Subgroup binary variable number (al) |
|---|---|---|---|---|---|---|
| **Congenital Heart Defects** | Q20-Q26 | 745, 746, 7470-7474 | Exclude PDA with GA <37 weeks<br>Exclude peripheral pulmonary artery stenosis with GA < 37 weeks | Q2111, Q250 if GA <37 weeks, Q2541, Q256 if GA<37 weeks, Q261 | Q250, 7470 if GA <37 weeks ** | al17 |
| Severe CHD | Q200, Q201, Q203, Q204, Q212, Q213, Q220, Q224, Q225, Q226, Q230, Q232, Q233, Q234, Q251, Q252, Q262 | 74500, 74510, 7452, 7453, 7456, 7461, 7462, 74600, 7463, 7465, 7466, 7467, 7471, 74720, 74742 | ICD9-BPA has no code for HRH and double outlet right ventricle | | | al97 |
| Common arterial truncus | Q200 | 74500 | | | | al18 |
| Double outlet right ventricle | Q201 | No code | | | | al109 |
| Transposition of great vessels | Q203 | 74510 | | | | al19 |
| Single ventricle | Q204 | 7453 | | | | al20 |
| VSD | Q210 | 7454 | | | | al21 |
| ASD | Q211 | 7455 | | Q2111 | | al22 |
| AVSD | Q212 | 7456 | | | | al23 |
| Tetralogy of Fallot | Q213 | 7452 | | | | al24 |
| Triscuspid atresia and stenosis | Q224 | 7461 | | | | al25 |
| Ebstein's anomaly | Q225 | 7462 | | | | al26 |
| Pulmonary valve stenosis | Q221 | 74601 | | | | al27 |
| Pulmonary valve atresia | Q220 | 74600 | | | | al28 |
| Aortic valve atresia/stenosis | Q230 | 7463 | ICD9-BPA has no code for atresia | | | al29 |
| Mitral valve anomalies | Q232, Q233 | 7465, 7466 | | | | al110 |
| Hypoplastic left heart | Q234 | 7467 | | | | al30 |
| Hypoplastic right heart | Q226 | No code | | | | al31 |
| Coarctation of aorta | Q251 | 7471 | | | | al32 |
| Aortic atresia / interrupted aortic arch | Q252 | 74720 | | | | al111 |
| Total anomalous pulm venous return | Q262 | 74742 | | | | al33 |
| PDA as **only** CHD in term infants (GA +37 weeks) | Q250 | 7470 | Livebirths only | | | al100 |
| **Respiratory** | Q300, Q32-Q34 | 7480, 7484, 74850, 74852, 74858, 7486, 7488 | Exclude Q336 | Q314, Q315, Q320, Q331 | Q309, 74819 | al34 |
| Choanal atresia | Q300 | 7480 | | | | al35 |
| Cystic adenomatous malf of lung | Q3380 | No code | | | | al36 |

| EUROCAT Subgroups | ICD10-BPA | ICD9-BPA | Comments | Excluded minor anomalies post-2005 | Excluded minor anomalies pre-2005 | Subgroup binary variable number (al) |
|---|---|---|---|---|---|---|
| **Oro-facial clefts** | Q35-Q37 | 7490, 7491, 7492 | Exclude association with holoprosencephaly or anencephaly subgroups | | | al101 |
| Cleft lip with or without cleft palate | Q36, Q37 | 7491, 7492 | Exclude association with holoprosencephaly or anencephaly subgroups | | | al102 |
| Cleft palate | Q35 | 7490 | Exclude association with cleft lip subgroup. Exclude association with holoprosencephaly or anencephaly subgroups | | | al103 |
| **Digestive system** | Q38-Q45, Q790 | 750, 751, 7566 | | Exclude Q381, Q382, Q3850, Q400, Q401, Q4021, Q430, Q4320, Q4381, Q4382 | Q381, Q401, 7500, 7506 | al40 |
| Oesophageal atresia with or without trachea-oesophageal fistula | Q390-Q391 | 75030-75031 | | | | al41 |
| Duodenal atresia or stenosis | Q410 | 75110 | Exclude if also annular pancreas subgroup | | | al42 |
| Atresia or stenosis of other parts of small intestine | Q411-Q418 | 75111-75112 | | | | al43 |
| Ano-rectal atresia and stenosis | Q420-Q423 | 75121-75124 | | | | al44 |
| Hirschsprung's disease | Q431 | 75130-75133 | | | | al45 |
| Atresia of bile ducts | Q442 | 75165 | | | | al46 |
| Annular pancreas | Q451 | 75172 | | | | al47 |
| Diaphragmatic hernia | Q790 | 75661 | | | | al48 |
| **Abdominal wall defects** | Q792, Q793, Q795 | 75671, 75670, 75679 | | | | al49 |
| Gastroschisis | Q793 | 75671 | | | | al50 |
| Omphalocele | Q792 | 75670 | | | | al51 |
| **Urinary** | Q60-Q64, Q794 | 75261, 753, 75672 | | Q610, Q627, Q633 | | al52 |
| *Bilateral* renal agenesis including Potter syndrome | Q601, Q606 | 75300 | Exclude unilateral | | | al53 |
| Multicystic renal dysplasia | Q6140, Q6141 | 75316 | | | | al54 |
| Congenital hydronephrosis | Q620 | 75320 | | | | al55 |
| Bladder exstrophy and / or epispadia | Q640, Q641 | 75261, 7535 | | | | al56 |
| Posterior urethral valve and / or prune belly | Q6420, Q794 | 75360, 75672 | | | | al57 |

| EUROCAT Subgroups | ICD10-BPA | ICD9-BPA | Comments | Excluded minor anomalies post-2005 | Excluded minor anomalies pre-2005 | Subgroup binary variable number (al) |
|---|---|---|---|---|---|---|
| **Genital** | Q50-Q52, Q54-Q56 | 7520-7524, 75260, 75262, 7527-7529 | | Q523, Q525, Q527, Q5520, Q5521 | Q540, 75260# | al58 |
| Hypospadias | Q54 | 75260 | | | Q540, 75260 | al59 |
| Indeterminate sex | Q56 | 7527 | | | | al60 |
| **Limb** | Q65-Q74 | 7543-7548, 755 | | Q653-Q656, Q662-Q669, Q670-Q678, Q680, Q6810, Q6821, Q683-Q685, Q7400 | 75432, 75452, 75460, 75473, 75481, 75560 | al61 |
| Limb reduction defects | Q71-Q73 | 7552-7554 | | | | al62 |
| Club foot – talipes equinovarus | Q660 | 75450 | | | | al66 |
| Hip dislocation and / or dyspasia | Q650-Q652, Q6580, Q6581 | 75430 | | | | al67 |
| Polydactyly | Q69 | 7550 | | | | al68 |
| Syndactyly | Q70 | 7551 | | | | al69 |
| **Other anomalies / syndromes** | | | | | | |
| Skeletal dysplasias | Q7402, Q77, Q7800, Q782-Q788, | No code | | | | al104 |
| Craniosynostosis | Q750 | 75600 | | | | al75 |
| Congenital constriction bands / amniotic band | Q7980 | 76280 | | | | al76 |
| Situs inversus | Q893 | 7593 | | | | al79 |
| Conjoined twins | Q894 | 7594 | | | | al80 |
| Congenital skin disorders | Q80-Q82 | 7571, 7573 | | Q825, Q8280 | Q825, Q8280, Q8281, 75731, 75738 | al81 |
| VATER/VACTERL | Q8726 | 759895 | | | | al112 |
| Vascular disruption anomalies | Q0435, Q411, Q412, Q418, Q710, Q712, Q713, Q720, Q722, Q723, Q730, Q793, Q795, Q7980, Q7982, Q8706 | No code | | | | al113 |
| Laterality anomalies | Q206, Q240, Q3381, Q890, Q893 | No code | | | | al114 |
| Teratogenic syndromes with malformations | Q86, P350, P351, P371 | No code | | | | al82 |
| Fetal alcohol syndrome | Q860 | 76076 | | | | al83 |
| Valproate syndrome | Q8680 | No code | | | | al84 |
| Maternal infections resulting in malformations | P350, P351, P371 | 7710, 7711, 77121 | | | | al86 |

## Appendix F. Pregnancy Outcome Definitions*

Pregnancy outcome: the end products of pregnancy which include three main categories:

- Fetal death, termination of pregnancy and live birth.
- Fetal death (intrauterine death, in utero death): death prior to complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of pregnancy; the death is indicated by the fact that after such separation the fetus does not show any evidence of life (WHO ICD 10).

Early fetal death (before 22 completed weeks of gestation) comprises ectopic pregnancy and miscarriage and late fetal death (after 22 completed weeks of gestation) is known as stillbirth.

- Ectopic pregnancy: extrauterine pregnancy, early fetal death most often in the Fallopian tube.
- Miscarriage: spontaneous abortion, molar pregnancy.
- Termination of pregnancy (induced abortion, elective abortion): artificial interruption of pregnancy.
- Live birth: the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy which, after such separation, breathes or shows any evidence of life. (WHO ICD 10).
- Gestational age or length: the duration of gestation is measured from the first day of the last normal menstrual period. Gestational age is expressed in completed days or completed weeks (eg, events occurring 280 to 286 days after the onset of the last menstrual period are considered to have occurred at 40 weeks of gestation).
- Last menstrual period (abbreviation LMP): according to international consensus, the gestational age is measured from the first day of the LMP.
- Birth weight: the initial weight of the infant at birth.
- Pre-term birth (previous term: premature birth): less than 37 completed weeks (less than 259 days) of gestation.

Term birth: from 37 to less than 42 completed weeks (259 to 293 days).

- Post-term birth: 42 completed weeks or more (294 days or more).
- Low birth weight: less than 2,500 gram (up to and including 2,499 g) of body weight of the newborn at birth.
- Intrauterine growth retardation (small for gestational age): the observed weight of a live born infant or size of a fetus is lower than expected on the basis of gestational age.

*EMEA/CHMP Guideline on Exposure to Medicinal Products During Pregnancy

## Appendix G. Template Summary Table of Pregnancy Outcome

| | Timing of Repatha® exposure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Unexposed (N = x) n (%) | Exposed but stopped prior to conception (N = x) n (%) | Exposure in 1st trimester (N = x) n (%) | Exposure in 2nd/3rd trimesters (N = x) n (%) | Exposed at conception and during 1st trimester but stopped in 2nd/3rd trimesters (N = x) n (%) | Exposed throughout pregnancy (N = x) n (%) | Exposure during breastfeeding only (N = x) n (%) | Exposure during both pregnancy and breastfeeding (N = x) n (%) |
| Pregnancies enrolled pre-partum | | | | | | | | |
| All outcomes | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Live birth without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Live birth with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Neonatal death without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Neonatal death with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Stillbirth without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Stillbirth with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Miscarriage without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Miscarriage with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Termination of pregnancy without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Termination of pregnancy with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Ectopic pregnancy | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Molar pregnancy | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Pregnancy continuing at time of data cut-off | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Pregnancies enrolled post-partum | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| All outcomes | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Live birth without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Live birth with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Neonatal death without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Neonatal death with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |

| | Timing of Repatha® exposure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Unexposed (N = x) n (%) | Exposed but stopped prior to conception (N = x) n (%) | Exposure in 1st trimester (N = x) n (%) | Exposure in 2nd/3rd trimesters (N = x) n (%) | Exposed at conception and during 1st trimester but stopped in 2nd/3rd trimesters (N = x) n (%) | Exposed throughout pregnancy (N = x) n (%) | Exposure during breastfeeding only (N = x) n (%) | Exposure during both pregnancy and breastfeeding (N = x) n (%) |
| **Stillbirth without congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Stillbirth with congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Miscarriage without congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Miscarriage with congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Termination of pregnancy without congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Termination of pregnancy with congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Ectopic pregnancy** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Molar pregnancy** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |

## Appendix H. Calculation of Percentage of Live Births

| Country | Live Births (2017) | % of Total live births | Expected N live births of unexposed mothers | Country cap on unexposed pregnancies |
|---|---|---|---|---|
| Australia | 309,142 | 8.0 | 48 | 150 |
| Austria | 87,633 | 2.3 | 14 | 136 |
| Belgium | 119,690 | 3.1 | 19 | 150 |
| Czech Republic | 114,405 | 3.0 | 18 | 150 |
| Denmark | 61,397 | 1.6 | 10 | 95 |
| Greece | 88,523 | 2.3 | 14 | 138 |
| Italy | 458,151 | 11.9 | 71 | 150 |
| Netherlands | 169,200 | 4.4 | 26 | 150 |
| Norway | 56,633 | 1.5 | 9 | 88 |
| Slovakia | 57,969 | 1.5 | 9 | 90 |
| South Africa | 989,318 | 25.6 | 154 | 150 |
| Spain | 390,024 | 10.1 | 61 | 150 |
| Sweden | 115,416 | 3.0 | 18 | 150 |
| Switzerland | 87,381 | 2.3 | 14 | 136 |
| UK | 755,043 | 19.6 | 117 | 150 |
| Total | 3,859,925 | 100.0 | 600 | NA[a] |

Sources:
Eurostat (2018) Live births and crude birth rate: https://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tps00204&plugin=1
Australian Bureau of Statistics (2018) Births, Australia, 2017:
http://www.abs.gov.au/ausstats%5Cabs@.nsf/0/8668A9A0D4B0156CCA25792F0016186A?Opendocument
Statistics South Africa (2018) Recorded live births, 2017. http://www.statssa.gov.za/?p=11478
Footnote:
[a] maximum number of unexposed pregnancies will be capped at 600 across all countries, therefore a minimum of 4 countries will be represented among unexposed pregnancies

# Appendix I. Pregnancy and Lactation Worksheets

## AMGEN® Pregnancy Notification Worksheet

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

SELECT OR TYPE IN A FAX#

### 1. Case Administrative Information

**Protocol/Study Number:** 20150162

**Study Design:** ☐ Interventional ■ Observational (If Observational: ☐ Prospective ☐ Retrospective)

### 2. Contact Information

**Investigator Name** _____ **Site #** _____

**Phone** (____) _____ **Fax** (____) _____ **Email** _____

**Institution** _____

**Address** _____

### 3. Subject Information

**Subject ID #** _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm ____ / dd ____ / yyyy ____

### 4. Amgen Product Exposure

| Amgen Product | Dose at time of conception | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm ____ /dd ____ /yyyy ____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ____ /dd ____ /yyyy ____

Did the subject withdraw from the study? ☐ Yes ☐ No

### 5. Pregnancy Information

Pregnant female's LMP mm ____ / dd ____ / yyyy ____ ☐ Unknown

Estimated date of delivery mm ____ / dd ____ / yyyy ____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm ____ / dd ____ / yyyy ____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ____ / dd ____ / yyyy ____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details: _____

**Form Completed by:**

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

Effective Date: March 27, 2011 Page 1 of 1

## AMGEN Lactation Notification Worksheet

*Fax Completed Form to the Country-respective Safety Fax Line*
SELECT OR TYPE IN A FAX# enter fax number

### 1. Case Administrative Information

**Protocol/Study Number:** 20150162

**Study Design:** ☐ Interventional ☑ Observational (If Observational: ☐ Prospective ☐ Retrospective)

### 2. Contact Information

**Investigator Name** _____ **Site #** _____

**Phone** (____)_____ **Fax** (____)_____ **Email** _____

**Institution** _____

**Address** _____

### 3. Subject Information

**Subject ID #** _____ **Subject Date of Birth:** mm____ / dd____ / yyyy____

### 4. Amgen Product Exposure

| Amgen Product | Dose at time of breast feeding | Frequency | Route | Start Date |
|---|---|---|---|---|
| | | | | mm____/dd____/yyyy____ |

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm____/dd____/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

### 5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

**Form Completed by:**

**Print Name:** _____ **Title:** _____

**Signature:** _____ **Date:** _____

Effective Date: 03 April 2012, version 2.

Page 1 of 1

**Amendment 1**

**Protocol Title: A Multinational Observational Study to Evaluate the Safety of Repatha® in Pregnancy**

Amgen Protocol Number Evolocumab 20150162

Amendment Date: 18 December 2018

**Rationale:**

This protocol is being amended to:

- Update the study design schema for clearer and more precise presentation
- Update the number of sites participating in the study (Section 9.2.2)
- Update inclusion criteria for subject eligibility regarding pregnancy identified retrospectively and multiple pregnancies (Section 9.2.3.1)
- Clarify study follow-up conditions and adverse event collection for pregnant or breastfeeding mothers who are exposed to Repatha®
- Group variables/data/outcomes to be collected into categories for better presentation
- Update the product indication in Section 7.1 (Diseases and Therapeutic Area) and Abstract
- Add relevant text to define the maximum size of the unexposed cohort overall, and to ensure geographical representativeness of the unexposed cohort (Section 9.5 and Appendix H)
- Update the stratified analyses for clearer description and more precise presentation
- Update safety reporting requirements (Section 11.2), by including a definition for Investigator Date of Awareness
- Update the template summary table of pregnancy outcome (Appendix G)
- Make editorial and administrative changes for grammatical reasons as well as for internal consistency within the protocol.

**Description of Changes:**

Section: Global

**Change:** The Amgen global version date was changed from 17 May 2016 to **18 December 2018**

Section: Global

**Change:** Editorial, typographical, and formatting changes were made throughout the document.

Section: Title Page, Summary Table of Study Protocol

**Replace:**

| | |
|---|---|
| Title | A Multinational Observational Study to Evaluate the Safety of Repatha® in Pregnancy |
| Protocol version identifier | 1.0 |
| Date of last version of the protocol | 17 May 2016 |
| EU Post Authorisation Study (PAS) Register No | Registration occurs after Amgen internal approval of the protocol; must be prior to commencement of first data capture |
| Active Substance | Evolocumab |
| Medicinal Product | Repatha® |
| Product Reference | EU/1/15/1016 |
| Procedure Number | EMA/H/C/3766 |
| Marketing Authorisation Holder(s) | Amgen Europe B.V. |
| Joint PASS | No |

| | |
|---|---|
| Research Question and Objectives | Research Question: To evaluate outcomes of pregnancy in females diagnosed with familial hypercholesterolaemia (FH), exposed to Repatha® during pregnancy. This includes follow-up of their infants to the age of 12 months.<br>Primary Objective: To describe congenital anomalies in infants of females with FH exposed to Repatha® within 15 weeks prior to or during pregnancy, followed to the age of 12 months.<br>Secondary Objectives: To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to and/or during pregnancy; To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to and/or during pregnancy; To describe outcomes (other than congenital anomalies) in infants up to the age of 12 months, born to females diagnosed with FH |
| Countries of Study | Europe (multicountry), South Africa, Australia |
| Author | PPD<br>Amgen Ltd<br>240 Science Park<br>Cambridge<br>CB4 0WD<br>UK |

Marketing Authorisation Holder

| | |
|---|---|
| Marketing authorisation holder(s) | Amgen Europe B.V. |
| MAH Contact | PPD<br>Amgen Ltd<br>Science Park<br>Cambridge<br>CB4 0WD<br>UK<br>PPD |

**With:**

| | |
|---|---|
| Title | A Multinational Observational Study to Evaluate the Safety of Repatha® in Pregnancy |
| Protocol version identifier | **2.0** |
| Date of last version of the protocol | 17 May 2016 |
| EU Post Authorisation Study (PAS) Register No | **EUPAS15153** |
| **NCT Number** | **NCT02906124** |
| Active Substance | Evolocumab |
| Medicinal Product | Repatha® |
| Product Reference | EU/1/15/1016 |
| Procedure Number | EMA/H/C/3766 |
| Marketing Authorisation Holder(s) | Amgen Europe B.V. |
| Joint PASS | No |
| Research Question and Objectives | Research Question: To evaluate **pregnancy and infant** outcomes **among** females diagnosed with familial hypercholesterolaemia (FH), exposed to Repatha® during pregnancy. This includes follow-up of their infants to the age of 12 months.<br>Primary Objective: To describe congenital anomalies in infants of females with FH exposed to Repatha® within 15 weeks prior to or during pregnancy, followed to the age of 12 months.<br>Secondary Objectives: To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to and/or during pregnancy; To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to and/or during pregnancy; To describe **health and developmental** outcomes in infants up to the age of 12 months, born to females diagnosed with FH **and exposed/unexposed to Repatha® during pregnancy and/or breastfeeding.** |
| Countries of Study | Europe (multicountry), South Africa, Australia |
| Author | PPD<br>Amgen Ltd<br>**1 Uxbridge Business Park**<br>**Sanderson Road**<br>**Uxbridge UB8 1DH**<br>UK |

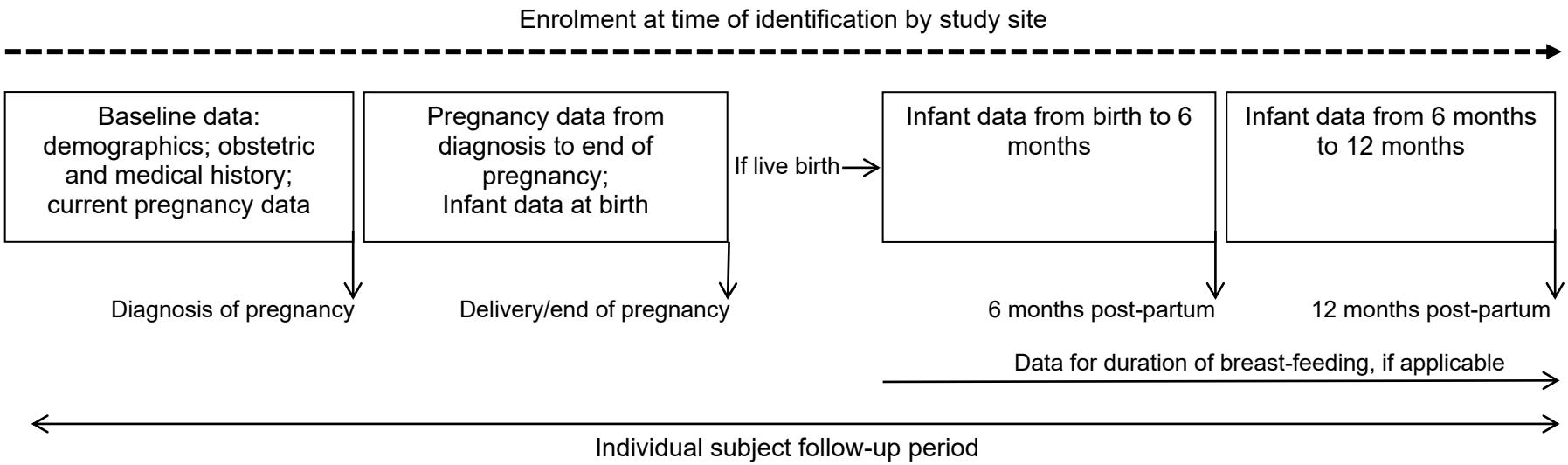
Marketing Authorisation Holder

| | |
|---|---|
| Marketing authorisation holder(s) | Amgen Europe B.V. |
| MAH Contact | PPD<br>Amgen Ltd<br>**1 Uxbridge Business Park**<br>**Sanderson Road**<br>**Uxbridge UB8 1DH**<br>UK<br>PPD |

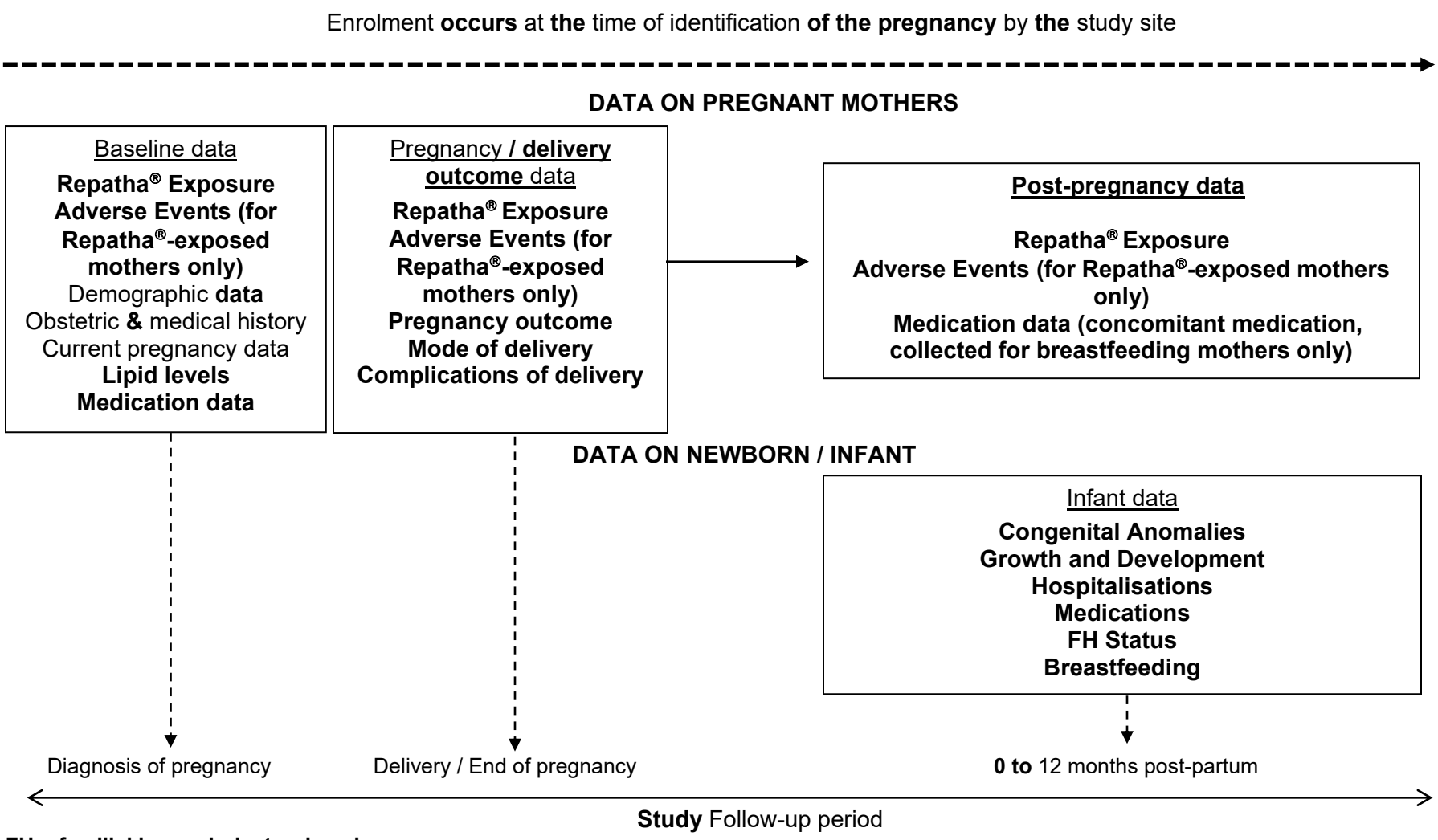
.

Section: Study Design Schema

**Replace:**



**With:**




**FH = familial hypercholesterolaemia**

Section: 4 Abstract, Study Background and Rationale, Paragraph 3

**Add:**

In Europe, Repatha® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated (Repatha® EPAR, EMA website). **Repatha is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies. Additionally, Repatha is indicated in adults with established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels, as an adjunct to correction of other risk factors: in combination with the maximum tolerated dose of a statin with or without other lipid-lowering therapies or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.**

Section: 4 Abstract, Study Background and Rationale, Paragraph 4

**Delete:**

Based on modality, mechanism of action, ~~published human data~~ and nonclinical studies, safety issues are not expected with Repatha® use during pregnancy.

Section: 4 Abstract, Study Background and Rationale, Paragraph 6

**Replace:**

Safety of Repatha® whilst breast-feeding is similarly considered to be missing information. Published literature support the expectation of a low risk of maternally-administered monoclonal antibodies resulting in pharmacologically relevant systemic exposures in breastfed infants, the milk-to-serum concentration ratio of IgG being low (Kim et al, 1992; Telemo et al., 1996; Ostensen and Eigenmann, 2004; Mahadevan et al, 2005; Vasiliauskas et al, 2006).

**With:**

**Similarly, s**afety of Repatha® whilst breast-feeding is considered to be missing information. Published literature **indicates that in general, there is** a low risk of maternally-administered monoclonal antibodies resulting in pharmacologically relevant systemic exposures in breastfed infants, the milk-to-serum concentration ratio of IgG being low (Kim et al, 1992; Telemo et al., 1996; Ostensen and Eigenmann, 2004; Mahadevan et al, 2005; Vasiliauskas et al, 2006).

Section: 4 Abstract, Study Background and Rationale, Paragraph 12

**Replace:**

This multinational observational study is expected to enrol female FH patients, identified in collaboration with specialist physicians and patient groups: Females with FH exposed to Repatha® during pregnancy and/or breast-feeding will form the exposed cohort, and females with FH unexposed to Repatha® during pregnancy and/or breast-feeding will form the internal comparator group. Although no formal comparison of exposed/unexposed subjects is planned, capturing outcomes of pregnancy in a rare population unexposed to Repatha® will provide some contemporary point of reference against which to consider outcomes in exposed pregnancies.

**With:**

This multinational observational study is expected to enrol female FH patients, identified in collaboration with specialist physicians and patient groups: Females with FH exposed to Repatha® during pregnancy and/or breast-feeding will form the exposed cohort, and females with FH unexposed to Repatha® during pregnancy and breast-feeding will form the internal comparator group. Although no formal comparison of exposed/unexposed subjects is planned, capturing outcomes of pregnancy in a rare population unexposed to Repatha® will provide contemporary reference **data** against which to consider outcomes in exposed pregnancies. **Due to potentially insufficient data and consequent lack of statistical power, it is unlikely that comparisons between the two groups will provide meaningful results, hence, no formal comparison of exposed/unexposed subjects is planned.**

Section: Abstract, Research Question and Objectives, Secondary Objectives

**Replace:**

- Secondary Objectives:

  To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to and/or during pregnancy

  - To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to and/or during pregnancy
  - To describe outcomes (other than congenital anomalies) in infants up to the age of 12 months, born to females diagnosed with FH and exposed/unexposed to Repatha®

**With:**

- Secondary Objectives:
  - To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to and/or during pregnancy
  - To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to and/or during pregnancy
  - To describe **health and developmental** outcomes in infants up to the age of 12 months, born to females diagnosed with FH and unexposed **or exposed** to Repatha® **during pregnancy and/or breastfeeding.**

Section: Abstract, Study Population or Data Resource

**Replace:**

The study population comprises females in Europe, South Africa and Australia diagnosed with FH and who are identified as being pregnant and/or breast-feeding during the study period, and who provide informed consent to participate in the study. Their infants will also be followed to the age of 12 months.

**With:**

The study population comprises females in Europe, South Africa and Australia diagnosed with FH and who are **either** pregnant or breast-feeding during the study period, and who provide informed consent to participate in the study**, if applicable according to local requirements**. Their infants will also be followed to the age of 12 months**, following consent by the mother (if applicable per local regulations)**.

**(Note: The therapeutic strategy assigned to each patient enrolled in the study will not be specified within this study protocol. Instead, it will be decided according to routine clinical practice, hence the decision for medicinal prescription will be clearly dissociated from the decision to include the patient in the study).**

Section: Abstract, Summary of Subject Eligibility Criteria, Inclusion Criteria

**Add:**

- Females diagnosed with FH
- Confirmed pregnancy during the study observation period
  - **Pregnancies identified retrospectively but within the study period will be included**
  - **Multiple pregnancies, occurring in the same woman within the study period, will all be included (as separate pregnancies)**
- Provided informed consent to follow-up in this study, for subject and their infant(s) born during the study observation period.

Section: Abstract, Variables

**Replace:**

- Outcome Variables:
  - Congenital anomaly including congenital abnormality or malformation as defined by EUROCAT (See Appendix E for full list)
  - Complications of pregnancy including:
    - Pre-eclampsia
    - Gestational diabetes
  - Outcomes of pregnancy: (See Appendix D for further definition):
    - Live birth
    - Elective termination (including reason, gestational age)
    - Miscarriage (including gender, anomalies, pathology)
    - Ectopic pregnancy
    - Molar pregnancy
    - Infant(s) gender; gestational age; birth weight, ; Apgar score
  - Mode of delivery:
    - Normal vaginal delivery
    - Operative vaginal delivery
    - Caesarian section
  - Complications of delivery:
    - Abnormal cord gas
    - Abnormal fetal heart rate auscultation
    - Abnormal amniotic fluid
    - Blood transfusion resulting from post-partum haemorrhage
    - Thromboembolism

- Exposure Variables:
  - Exposure to Repatha® (duration of exposure, doses, dose frequency) within 15 weeks prior to conception and/or during pregnancy and/or whilst breast-feeding
- Other Variables:
  - Baseline:
    - Country of residence; age; education; occupation; height and weight
    - Current pregnancy history (date of last menstrual period; estimated date of delivery; number of fetuses; treatment for infertility)
    - Medical history (FH diagnosis; significant comorbid conditions; family history of congenital disorders)
    - Obstetric history (number of previous pregnancies and outcome; previous maternal pregnancy complications; previous fetal/neonatal abnormalities; history of subfertility)
  - Medications (product, dose, dose dates) taken within 3 months prior to or during pregnancy (excluding medication routinely administered during labour/delivery) and/or breast-feeding
  - Lipid levels (total cholesterol, LDL, HDL, triglycerides)
  - Infant development milestones and health to 12 months of age (growth, hospitalisation, chronic medication)

**With:**

**The following types of data/outcomes will be collected:**

- **Maternal Data:**
  - **Demographics**
  - **Current pregnancy history**
  - **Medical history**
  - **Obstetric history**
  - **Lipid levels**
  - **Medications**
  - Congenital anomal**ies**
  - Complications of pregnancy
  - Outcomes of pregnancy
  - Mode of delivery
  - Complications of delivery
- **Infant Data:**
  - **Infant status at delivery**
  - **Infant health, growth, and developmental outcomes until 12 months of age**

– Exposure **Data: Exposure** to Repatha® (duration of exposure, doses, dose frequency) within 15 weeks prior to conception and/or during pregnancy and/or whilst breast-feeding

Section: Abstract, Study Sample Size

**Add:**

The Guideline further states that if no increased incidence of malformations is observed within at least 300 first trimester-exposed, prospectively collected pregnancies with known pregnancy outcomes (births or fetopathological examinations) then the conclusion might be reached that the medicinal product is not responsible for a 10-fold or more increase of the overall incidence of malformations. In accordance with the Guideline, this study will endeavour to enrol 300 pregnancies exposed to Repatha in the first trimester. **The maximum number of unexposed pregnancies will be limited to a ratio of 2 unexposed to 1 exposed; ie, 600 unexposed pregnancies.**

Section: 5 Amendments and Updates

**Replace:**

None

**With:**

| **Amendment/Update** | **Date Performed** |
|---|---|
| **Study Protocol Amendment 1** | **18 December 2018** |

Section: 7.1 Diseases and Therapeutic Area, Paragraph 3

**Replace:**

In Europe, Repatha® is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet, in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or, alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated (Repatha® EPAR, EMA website). Based on modality, mechanism of action, published human data and nonclinical studies, safety issues are not expected with Repatha® use during pregnancy.

**With:**

In Europe, Repatha® is indicated in adults with **established atherosclerotic cardiovascular disease (myocardial infarction, stroke or peripheral arterial disease) to reduce cardiovascular risk by lowering LDL-C levels**, as an adjunct to **correction of other risk factors:** in combination with the maximum tolerated dose of a statin with **or without** other lipid-lowering therapies **or, alone or in combination with other lipid-lowering therapies** in patients who are statin-intolerant, or for whom a statin is contraindicated. **Repatha is also indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies** (Repatha® EPAR, EMA website)**.** Based on modality, mechanism of action, and nonclinical studies, safety issues are not expected with Repatha® use during pregnancy.

Section: 7.1 Diseases and Therapeutic Area, Paragraph 6

**Replace:**

Safety of Repatha® whilst breast-feeding is similarly considered to be missing information. Published literature support that there is a low risk of maternally-administered monoclonal antibodies resulting in pharmacologically relevant systemic exposures in breastfed infants, the milk-to-serum concentration ratio of IgGs being low (Kim et al, 1992; Telemo et al., 1996; Ostensen and Eigenmann, 2004; Mahadevan et al, 2005; Vasiliauskas et al, 2006).

**With:**

**Similarly, s**afety of Repatha® whilst breast-feeding is considered to be missing information. Published literature **indicates** that **in general,** there is a low risk of maternally-administered monoclonal antibodies resulting in pharmacologically relevant systemic exposures in breastfed infants, the milk-to-serum concentration ratio of IgGs being low (Kim et al, 1992; Telemo et al., 1996; Ostensen and Eigenmann, 2004; Mahadevan et al, 2005; Vasiliauskas et al, 2006).

Section: 7.2 Rationale, Paragraph 4

**Replace:**

This multinational observational study is expected to enrol female FH patients, identified in collaboration with specialist physicians and patient groups: Females with FH exposed to Repatha® during pregnancy and/or breast-feeding will form the exposed cohort, and

females with FH unexposed to Repatha® during pregnancy and/or breast-feeding will form the internal comparator group. Although no formal comparison of exposed/unexposed subjects is planned, capturing outcomes of pregnancy in a rare population unexposed to Repatha® will provide some contemporary point of reference against which to consider outcomes in exposed pregnancies.

**With:**

This multinational observational study is expected to enrol female FH patients, identified in collaboration with specialist physicians and patient groups:

- Females with FH exposed to Repatha® during pregnancy and/or breast-feeding will form the exposed cohort, and
- Females with FH unexposed to Repatha® during pregnancy and breast-feeding will form the internal comparator group. Although no formal comparison of exposed/unexposed subjects is planned, capturing outcomes of pregnancy in a rare population unexposed to Repatha® will provide contemporary reference data against which to consider outcomes in exposed pregnancies.

Section: 8.2 Secondary Objectives

**Replace:**

- To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to or during pregnancy
- To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to or during pregnancy
- To describe outcomes (other than congenital anomalies) in infants up to the age of 12 months, born to females diagnosed with FH and exposed/unexposed to Repatha®

**With:**

- To describe outcomes of pregnancy (other than congenital anomalies) in females with FH exposed to Repatha® within 15 weeks prior to or during pregnancy
- To describe outcomes of pregnancy in females with FH not exposed to Repatha® within 15 weeks prior to or during pregnancy
- To describe **health and developmental** outcomes in infants up to the age of 12 months, born to females diagnosed with FH and **unexposed or** exposed to Repatha® **during pregnancy and/or breastfeeding.**

Section: 9.1 Study Design, Paragraph 1, 3, and 4

**Replace:**

The study is a multinational (Europe, South Africa and Australia) prospective observational cohort study designed to capture data on outcomes of pregnancy in women diagnosed with FH. Within this population, the exposure of interest is administration of Repatha® during pregnancy and/or breast-feeding. The primary and secondary outcome measures are congenital anomaly and other outcomes of pregnancy, respectively.

At the individual subject level, data of interest include demographics, medical and obstetric history at the time of confirmation of pregnancy within the study observation period. The subject will be followed for the outcome of pregnancy, including follow-up of the infant(s) to 12 months post-delivery. Data capture may be retrospective if a pregnancy occurring during the study period is detected after delivery.

Study site staff will abstract data from patient notes and entered into the sponsor's electronic database. There will be independent external expert adjudication of adverse outcomes (particularly those associated with congenital anomaly), to ensure consistency and accuracy of reporting. Analyses will be conducted by the sponsor.

**With:**

The study is a multinational (Europe, South Africa and Australia) prospective observational cohort study designed to capture data on outcomes of pregnancy in women diagnosed with FH. Within this population, the exposure of interest is administration of Repatha® during pregnancy and/or breast-feeding. The primary and secondary outcome measures are congenital anomaly and other outcomes of pregnancy **or infancy**, respectively.

At the individual subject level, data of interest include demographics, medical and obstetric history at the time of confirmation of pregnancy within the study observation period. The subject will be followed **to determine** the outcome of pregnancy, including follow-up of the infant(s) to 12 months post-delivery. Data capture may be retrospective if a pregnancy occurring during the study period is detected after delivery.

Study site staff will abstract data from patient notes and entered into the sponsor's electronic database. There will be independent external expert adjudication of

congenital anomaly to ensure consistency and accuracy of reporting. Analyses will be conducted by the sponsor.

Section: 9.2.2 Selection and Number of Sites, Paragraph 2

**Replace:**

At least 70 sites are expected to participate in the study. As many countries as possible within Europe, as well as South Africa and Australia, are invited and encouraged to participate. Site identification is expected to continue during the course of the study, to maximise the catchment across the FH population and hence the number of potential study subjects.

**With:**

**An estimated 50 to** 70 sites are expected to participate in the study. As many countries as possible within Europe, as well as South Africa and Australia, are invited and encouraged to participate. Site identification is expected to continue during the course of the study, to maximise the catchment across the FH population and hence the number of potential study subjects.

Section: 9.2.3.1 Inclusion Criteria

**Add:**

- Females diagnosed with FH
- Confirmed pregnancy during the study observation period
  - **Pregnancies identified retrospectively but within the study period will be included**
  - **Multiple pregnancies, occurring in the same woman within the study period, will all be included (as separate pregnancies)**
- Provided informed consent to follow-up in this study, for subject and their infant(s) born during the study observation period

Section: 9.2.6 Study Follow-up

**Replace:**

Follow-up duration may differ for each individual subject, depending on the outcome of pregnancy: Initial baseline information will be recorded at confirmation of pregnancy and the subject will be followed for outcome of pregnancy. Information on pregnancy outcome, and on infant health at 6 and 12 months after delivery, will be captured. In addition, data will be captured for the duration of breast-feeding, if applicable.

**With:**

Follow-up duration may differ for each individual subject, depending on the outcome of pregnancy: Initial baseline information will be recorded at confirmation of pregnancy and the subject will be followed for outcome of pregnancy **and, if breastfeeding following a live birth, until termination of breastfeeding**. Information on pregnancy outcome, and on infant health **and development up to** 12 months after delivery, will be captured.

Section: 9.3 Outcomes - Variables

**Replace:**

9.3 Variables

Primary and secondary outcome variables include:

- Outcome Variables:
  - Congenital anomaly including congenital abnormality or malformation as defined by EUROCAT (See Appendix E for full list)
  - Complications of pregnancy including:
    - Pre-eclampsia
    - Gestational diabetes
  - Outcomes of pregnancy: (See Appendix F for further definition):
    - Live birth
    - Elective termination (including reason, gestational age)
    - Miscarriage (including gender, anomalies, pathology)
    - Ectopic pregnancy
    - Molar pregnancy
    - Infant(s) gender; gestational age; birth weight; Apgar score
  - Mode of delivery:
    - Normal vaginal delivery
    - Operative vaginal delivery
    - Caesarian section
  - Complications of delivery:
    - Abnormal cord gas
    - Abnormal fetal heart rate
    - Abnormal amniotic fluid
    - Blood transfusion resulting from post-partum haemorrhage;
    - Thromboembolism

- Exposure Variables:
  - Exposure to Repatha® (duration of exposure, doses, dose dates) within 15 weeks prior to conception and/or during pregnancy and/or whilst breast-feeding. In adult subjects a single dose of Repatha® constitutes exposure. In infants, exposure may occur in utero and/or via breast milk, within 15 weeks following the date of Repatha® dosing in the mother.
- Other Variables:
  - Baseline:
    - Country of residence; age; education; occupation; height and weight
    - Current pregnancy history (date of last menstrual period; estimated date of delivery; number of fetuses; treatment for infertility)
    - Medical history (FH diagnosis; significant comorbid conditions; family history of congenital disorders)
    - Obstetric history (number of previous pregnancies and outcome; previous maternal pregnancy complications; previous fetal/neonatal abnormalities; history of subfertility)
  - Medications (product, dose, dose dates) taken within 3 months prior to or during pregnancy (excluding medication routinely administered during labour/delivery) and/or breast-feeding
  - Lipid levels (total cholesterol, LDL, HDL, triglycerides)
  - Infant development milestones and health to 12 months of age (growth, hospitalisation, chronic medication)

Information available for each subject on all variables will be reported by study site staff in the study-specific sponsor database. The original data source will be patient records, from routine follow-up of subjects.

**With:**

### 9.3 Outcomes - Variables

**Information available for each subject on all variables will be reported by study site staff in the study-specific database held by the sponsor. The original data source will be patient (maternal – infant) records, from routine follow-up of subjects:**

- **Maternal Data:**
  - **Demographics:**
    - **Country of residence**
    - **Age (at start of pregnancy, categorized into ≤ 19, 20-24, 25-29, 30-34, 35-39, 40-44, ≥ 45 year age categories)**
    - **Education (highest level)**

- **Occupation**
- **Height and weight (to calculate body mass index, categorised into < 20, 20-24, 25-29, ≥ 30 kg/m$^2$ body mass index categories)**

– **Current pregnancy history:**
- **Date of last menstrual period**
- **Estimated date of delivery**
- **Number of fetuses**
- **Treatment for infertility**

– **Medical history:**
- **FH diagnosis status and method of diagnosis**
- **Presence of significant comorbid conditions (hypertension, diabetes mellitus, epilepsy, other)**
- **Family history of congenital disorders**

– **Obstetric history:**
- **Number of previous pregnancies and outcome**
- **Previous maternal pregnancy complications**
- **Previous fetal/neonatal abnormalities**
- **History of subfertility**

– **Medications (product, dose, dose dates) taken within 3 months prior to or during pregnancy (excluding medication routinely administered during labour/delivery) and/or breast-feeding**

– **Lipid levels (triglycerides, total cholesterol, LDL-C, HDL-C)**

– **Congenital anomaly including congenital abnormality or malformation as defined by European Surveillance of Congenital Anomalies (EUROCAT) (See Appendix E for full list)**

– **Complications of pregnancy:**
- **Pre-eclampsia**
- **Gestational diabetes**

– **Outcomes of pregnancy: (See Appendix F for further definition):**
- **Live birth (with / without congenital anomaly)**
- **Neonatal death (with / without congenital anomaly)**
- **Stillbirth (with / without congenital anomaly)**
- **Elective termination (with / without congenital anomaly)**
- **Miscarriage (with / without congenital anomaly)**
- **Spontaneous abortion**
- **Ectopic pregnancy**
- **Molar pregnancy**

- **Mode of delivery:**
  - **Normal vaginal delivery**
  - **Operative vaginal delivery**
  - **Vaginal breech delivery**
  - **Caesarean section**
- **Complications of delivery:**
  - **Abnormal Cord gas**
  - **Fetal heart rate abnormalities**
  - **Abnormal amniotic fluid**
  - **Blood transfusion resulting from post-partum haemorrhage;**
  - **Thromboembolism**

- **Infant Data:**
  - **Infant status at delivery:**
    - **Infant(s) sex**
    - **Gestational age**
    - **Birth weight**
    - **Apgar score**
  - **Infant outcomes until 12 months of age:**
    - **Weight growth**
    - **Developmental delay (not meeting the usual developmental milestones during the first 12 months of age)**
    - **Hospitalisations (total number of days hospitalised; number of hospitalisation episodes during the first 12 months)**
    - **Chronic medication (defined as medication prescribed for a period of 4 weeks or more)**
    - **Breastfeeding (date of start/stop, exclusive breastfeeding [Yes/No])**
- Exposure Variables:
  - Exposure to Repatha® (duration of exposure, doses, dose dates) within 15 weeks prior to conception and/or during pregnancy and/or whilst breast-feeding. In adult subjects a single dose of Repatha® constitutes exposure. In infants, exposure may occur in utero and/or via breast milk, within 15 weeks following the date of Repatha® dosing in the mother.

Section: 9.3.1 Exposure Assessment, Paragraph 2 and 3

**Add:**

Exposure to Repatha® in the 15 weeks (i.e., 5 half-lives of Repatha®) prior to or during pregnancy or breast-feeding will be entered by site staff into study-specific electronic case report forms and will be reported descriptively by dose and dates of administration. Exposure will be counted in doses of Repatha®.

**The study population comprises females in Europe, South Africa and Australia diagnosed with FH and who are either pregnant or breast-feeding during the study period, and who provide informed consent to participate in the study, if applicable according to local requirements. Their infants will also be followed to the age of 12 months, following consent by the mother (if applicable per local regulations).**

**(Note: The therapeutic strategy assigned to each patient enrolled in the study will not be specified within this study protocol. Instead, it will be decided according to routine clinical practice, hence the decision for medicinal prescription will be clearly dissociated from the decision to include the patient in the study).**

Section: 9.5 Study Size

**Add:**

In accordance with the Guideline, this study will endeavour to enrol 300 pregnancies exposed to Repatha in the first trimester **in order to meet the primary objective of this study. The maximum number of unexposed pregnancies will be limited to a ratio of 2 unexposed to 1 exposed; ie, the maximum will be 600 unexposed pregnancies. In addition, the maximum of unexposed pregnancies originating from a single country will be limited to the minimum of N = 150 or tenfold the expected proportion of births out of the combined total of live births as reported by the relevant Bureaus of Statistics in the participating countries (Appendix H). For example, the observed number of live births in Norway in 2017 represented 1.5% of the births across all participating countries. Therefore, no more than N = 88 (10 x 1.5% = 15% of 600) unexposed pregnancies will originate from Norway. The observed number of United Kingdom births represents 19.6% of all 2017 live births across all countries; tenfold 19.6% of 600 would exceed the target of 600, therefore the number of unexposed pregnancies from the United Kingdom will be capped at N=150. This will ensure we enrol as many unexposed pregnancies as possible whilst avoiding that unexposed pregnancies will originate from a single country only.**

Section: 9.7.1.1 Interim Analyses

**Replace:**

**9.7.1.1 Interim Analysis/Analyses**

No formal interim analyses are planned. However, the appropriate regulatory authorities will receive:

- Interim reports of all analyses performed, to be submitted annually. (See Appendix G for the template Summary Table to be included in the report)
- A feasibility report three years after study commencement, summarising the number of subjects enrolled, any exposure to Repatha® and describing primary and secondary outcome data.

**With:**

**9.7.1.1 Interim Analyses**

**T**he appropriate regulatory authorities will receive:

- Interim reports of all analyses performed, to be submitted annually. (See Appendix G for an example Summary Table template to be included in the report)
- A feasibility report three years after study commencement, summarising the number of subjects enrolled, any exposure to Repatha® and describing primary and secondary outcome data.

Section: 9.7.2.1 General Considerations, Paragraph 4

**Add:**

**Multiple pregnancies, occurring in the same woman within the study period, will be reported as separate pregnancies (with an addition of a relevant footnote in the respective tables, indicating that two or more pregnancies occurred in the same woman).**

Section: 9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

**Replace:**

For all study-related parameters, data are recorded as part of pregnancy follow-up in this cardiovascular high risk population, and a high degree of completeness of follow-up and data recording can be expected. Proactive follow-up will also be encouraged.

There will be no imputation for missing data.

**With:**

For all study-related parameters, data are recorded as part of pregnancy follow-up in this cardiovascular high-risk population, and a high degree of completeness of follow-up and data recording can be expected. **However, the necessity of obtaining data from multiple sources may incur an increased risk of being unable to obtain specific sets of patient notes.** Proactive follow-up will also be encouraged.

There will be no imputation **of** missing data.

Section: 9.7.2.4 Analysis of the Primary and Secondary Endpoints

**Replace:**

Analysis of Primary Objective:

Congenital anomalies will be summarised and descriptive statistics will be presented.

Congenital anomalies will be defined according to ICD10-BPA codes.

Analyses of Secondary Objectives:

Secondary objective outcome measures will be summarised and descriptive statistics will be presented.

For all analyses, outcomes of Repatha®-exposed pregnancy in women with FH (and their infants) and enrolled into this study may be compared to:

- Outcomes in women with FH (and their infants) with pregnancies not exposed to Repatha® and enrolled into this study, overall and stratified by lipid lowering therapy use
- Outcomes documented in existing data sources which may include: A female heterozygous FH population in Norway; European teratology information centres; the general population in the EU; a systematic review of the literature to capture any additional published pregnancy outcome rates in the population of interest.

**With:**

Analysis of Primary Objective:

Congenital anomalies will be summarised and descriptive statistics will be presented.

Congenital anomalies will be defined according to ICD10-BPA codes **(codes included in Appendix E: EUROCAT Subgroups of Congenital Anomalies)**.

Analyses of Secondary Objectives:

Secondary objective outcome measures will be summarised and descriptive statistics will be presented.

**Due to potentially insufficient data and consequent lack of statistical power, it is unlikely that comparisons between the 2 groups will provide meaningful results, hence, no formal comparison of exposed/unexposed subjects is planned.**

Section: 9.7.2.7 Stratified Analysis

**Replace:**

Analyses will be stratified according to exposure to Repatha® (in the 15 weeks prior to conception or in the first trimester of pregnancy, in the second or third trimester of pregnancy, and/or whilst breast-feeding), vs unexposed, and by exposure to other lipid modifying therapies (including statins, PCSK9 inhibitors, CETP inhibitors, and others).

**With:**

**For the secondary objective of describing health and developmental outcomes in infants up to 12 months of age, a**nalyses will be stratified according to **whether the infant was** expos**ed** to Repatha® (in the 15 weeks prior to conception or in the first trimester of pregnancy, in the second or third trimester of pregnancy, and/or whilst breast-feeding)**. In addition, a stratified analysis will be conducted** by exposure to other lipid modifying therapies (including statins, PCSK9 inhibitors, CETP inhibitors, and others).

**In addition, data obtained from retrospective and prospective subject identification will be reported separately (to account for the possibility that subjects enrolled retrospectively may differ from those enrolled prospectively).**

**Results from mothers are to be presented using the following columns: (i) 'unexposed', (ii) 'exposed but stopped prior to conception', (iii) 'exposure in 1st trimester (up to 15 weeks)', (iv) 'exposure in 2nd/3rd trimesters', (v) 'exposed at conception and during 1st trimester but stopped during 2nd/3rd trimesters, (vi) 'exposed throughout pregnancy', (vii) 'exposure during breastfeeding only', and (viii) 'exposure anytime during pregnancy and up to 15 weeks, and breastfeeding'. Columns will not be mutually exclusive.**

Section: 9.9.1 Information Bias

**Replace:**

Information bias is unlikely, as the key outcome measures are objective and the primary outcome measure will be independently adjudicated. There is no reason to anticipate any differential in the reporting of outcomes between exposed and unexposed subjects enrolled into the study.

**With:**

Information bias **may occur from participants who are recruited retrospectively more likely to have adverse outcomes. This will occur because participants with adverse outcomes will make the clinician consider recruiting them.**

Section: 9.9.2 Selection Bias, Paragraph 2

**Add:**

**Selection bias may occur due to pregnant women without adverse outcomes potentially being less likely to be told about the study, or less inclined to participate in the study.** To help to minimi**s**e selection bias arising from preferential enrolment of subjects experiencing adverse outcomes rather than those with normal outcomes, sites will be requested to enrol all eligible patients whether retrospectively or prospectively identified, and regardless of outcomes which are already known.

Section: 9.9.3 Limitations due to Missing Data and/or Incomplete Data

**Add:**

**Although the necessity of obtaining data from multiple sources may incur an increased risk of being unable to obtain specific sets of patient notes,** **m**issing/incomplete data is unlikely to be a limitation for subjects identified and enrolled into this study, as physicians treating FH women pay particular attention to their clinical management during pregnancy and breast-feeding. It is not expected that information on outcomes will be missing, due to the critical nature of follow-up of pregnant women and their infants regardless of an adverse or a normal outcome. Additionally, Amgen will review all study data thoroughly and will follow up directly with study sites to query for missing information.

Section: 10.1 Informed Consent, Paragraph 1

**Add:**

An initial sample informed consent form is provided for the Investigator to prepare the informed consent document to be used at his or her site**, according to local regulations**. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the Investigator. The written informed consent document is to be prepared in the language(s) of the potential subject population.

Section: 11 Collection of Safety Information and Product Complaints, Paragraph 2

**Add:**

For subjects known to be exposed to Repatha® within the 15 weeks prior to or during pregnancy and/or during breastfeeding, a Pregnancy Notification Worksheet and/or Lactation Notification Worksheet (Appendix H), as appropriate, is to be submitted to Amgen **and will be collected until termination of breastfeeding, otherwise until 12 months post-partum**.

Section: 11.2 Safety Reporting Requirements, Paragraph 1 and 2

**Replace:**

The Investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the Investigator or reported by the subject that occur during the observation period through to the final study contact are recorded in the subject's appropriate study documentation. Safety events must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness.

**With:**

The Investigator is responsible for ensuring that safety events (adverse events, product complaints and other safety findings) observed by the Investigator or reported by the subject that occur during the **study** observation period are recorded in the subject's appropriate study documentation. **The observation period for this study consists of 2 distinct periods: 1) the retrospective observation period that is defined as the time between diagnosis of pregnancy and the subject's enrolment into the study and, 2) the prospective observation period defined as the time between subject's enrolment date until the end of her and the infant's follow-up.**

**For safety events that occurred in the retrospective observation period, the date on which the investigator accessed the subject's medical charts to abstract the relevant retrospective information should be entered into the field "Date Investigator became aware of this Event" on the Event eCRF.** Safety events **identified in both the retrospective and prospective period** must be submitted as individual case safety reports to Amgen via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of Investigator awareness.
**Non-serious adverse events must be reported in an expeditious manner, not to exceed 15 calendars days of investigator awareness.**

Section: 15 Appendices, Appendix G, Template Summary Table of Pregnancy Outcome

**Replace:**

| Pregnancy outcome | Prospective cases Number | | | | | Retrospective cases Number | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Timing of exposure in pregnancy | | | | | Timing of exposure in pregnancy | | | | |
| | Before conception | 1st trimester | After 1st trimester | During all pregnancy | Unknown | Before conception | 1st trimester | After 1st trimester | During all pregnancy | Unknown |
| Ectopic pregnancy | | | | | | | | | | |
| Spontaneous abortion | | | | | | | | | | |
| Elective termination (foetal defects) | | | | | | | | | | |
| Elective termination (no foetal defects or unknown) | | | | | | | | | | |
| Stillbirth with foetal defects | | | | | | | | | | |
| Stillbirth without foetal defects | | | | | | | | | | |
| Live birth with congenital anomaly | | | | | | | | | | |
| Live birth without congenital anomaly | | | | | | | | | | |
| Total | | | | | | | | | | |

**With:**

| | Timing of Repatha® exposure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Unexposed (N = x) n (%) | Exposed but stopped prior to conception (N = x) n (%) | Exposure in 1st trimester (N = x) n (%) | Exposure in 2nd/3rd trimesters (N = x) n (%) | Exposed at conception and during 1st trimester but stopped in 2nd/3rd trimesters (N = x) n (%) | Exposed throughout pregnancy (N = x) n (%) | Exposure during breastfeeding only (N = x) n (%) | Exposure during both pregnancy and breastfeeding (N = x) n (%) |
| Pregnancies enrolled pre-partum | | | | | | | | |
| All outcomes | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Live birth without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Live birth with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Neonatal death without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Neonatal death with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Stillbirth without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Stillbirth with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Miscarriage without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Miscarriage with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Termination of pregnancy without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Termination of pregnancy with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Ectopic pregnancy | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Molar pregnancy | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Pregnancy continuing at time of data cut-off | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Pregnancies enrolled post-partum | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| All outcomes | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Live birth without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Live birth with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Neonatal death without congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| Neonatal death with congenital anomaly | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |

| | Timing of Repatha® exposure | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | Unexposed (N = x) n (%) | Exposed but stopped prior to conception (N = x) n (%) | Exposure in 1st trimester (N = x) n (%) | Exposure in 2nd/3rd trimesters (N = x) n (%) | Exposed at conception and during 1st trimester but stopped in 2nd/3rd trimesters (N = x) n (%) | Exposed throughout pregnancy (N = x) n (%) | Exposure during breastfeeding only (N = x) n (%) | Exposure during both pregnancy and breastfeeding (N = x) n (%) |
| **Stillbirth without congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Stillbirth with congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Miscarriage without congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Miscarriage with congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Termination of pregnancy without congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Termination of pregnancy with congenital anomaly** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Ectopic pregnancy** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |
| **Molar pregnancy** | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) | x (x.x) |

Section: 15 Appendices, Appendix H, Calculation of Percentage of Live Births

**Add:**

## Appendix H. Calculation of Percentage of Live Births

| Country | Live Births (2017) | % of Total live births | Expected N live births of unexposed mothers | Country cap on unexposed pregnancies |
|---|---|---|---|---|
| Australia | 309,142 | 8.0 | 48 | 150 |
| Austria | 87,633 | 2.3 | 14 | 136 |
| Belgium | 119,690 | 3.1 | 19 | 150 |
| Czech Republic | 114,405 | 3.0 | 18 | 150 |
| Denmark | 61,397 | 1.6 | 10 | 95 |
| Greece | 88,523 | 2.3 | 14 | 138 |
| Italy | 458,151 | 11.9 | 71 | 150 |
| Netherlands | 169,200 | 4.4 | 26 | 150 |
| Norway | 56,633 | 1.5 | 9 | 88 |
| Slovakia | 57,969 | 1.5 | 9 | 90 |
| South Africa | 989,318 | 25.6 | 154 | 150 |
| Spain | 390,024 | 10.1 | 61 | 150 |
| Sweden | 115,416 | 3.0 | 18 | 150 |
| Switzerland | 87,381 | 2.3 | 14 | 136 |
| UK | 755,043 | 19.6 | 117 | 150 |
| Total | 3,859,925 | 100.0 | 600 | NA[a] |

Sources:
Eurostat (2018) Live births and crude birth rate: https://ec.europa.eu/eurostat/tgm/table.do?tab=table&init=1&language=en&pcode=tps00204&plugin=1
Australian Bureau of Statistics (2018) Births, Australia, 2017:
http://www.abs.gov.au/ausstats%5Cabs@.nsf/0/8668A9A0D4B0156CCA25792F0016186A?Opendocument
Statistics South Africa (2018) Recorded live births, 2017. http://www.statssa.gov.za/?p=11478
Footnote:
[a] maximum number of unexposed pregnancies will be capped at 600 across all countries, therefore a minimum of 4 countries will be represented among unexposed pregnancies