1. ABSTRACT

- **Title**

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

- **Keywords**

pregnancy, registry, familial hypercholesterolaemia

- **Rationale and Background**

This study was conducted in response to a request by the European Medicines Agency (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 breastfeeding.

- **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.

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 exposed/unexposed to Repatha during pregnancy and/or breastfeeding

- **Study Design**

Multinational prospective observational cohort study.

- **Setting**

Sites in Europe and Australia where pregnant FH patients are treated, including national or regional FH referral centres, or other specialist sites which treat FH patients.

Data was planned to be captured for pregnancies occurring between June 2016 and June 2026. The first subject was enrolled on 12 January 2017. Due to a limited number of subjects, the registry was discontinued, following agreement from the EMA. The last subject was enrolled on 12 October 2020 and the last subject completed the study on 06 November 2020.

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

Subjects were females diagnosed with FH, with a confirmed pregnancy during the study observation period and who provided informed consent to follow-up in this study, for themselves and their infant(s) born during the study observation period. The study planned to enroll 300 pregnancies exposed to Repatha in the first trimester.

- **Variables and Data Sources**

Outcome variables included:

  - congenital anomaly including congenital abnormality or malformation as defined by European Surveillance of Congenital Anomalies (EUROCAT)

- complications of pregnancy
- outcomes of pregnancy
- mode of delivery
- complications of delivery

Exposure Variables:

Exposure to Repatha (duration of exposure, doses, dose dates) within 15 weeks prior to conception and/or during pregnancy and/or whilst breastfeeding. In adult subjects a single dose of Repatha constituted exposure. In infants, exposure could have occurred in utero and/or via breast milk, within 15 weeks following the date of Repatha dosing in the mother.

Other Variables:

- demographics
- medical, obstetric and pregnancy history
- medications (product, dose, dose dates) taken within 3 months prior to or during pregnancy (excluding medication routinely administered during labour/delivery) and/or breastfeeding
- lipid levels (total cholesterol, low density lipoprotein-cholesterol (LDL-C), high density lipoprotein, triglycerides)
- infant development milestones and health to 12 months of age (growth, hospitalisation, chronic medication)

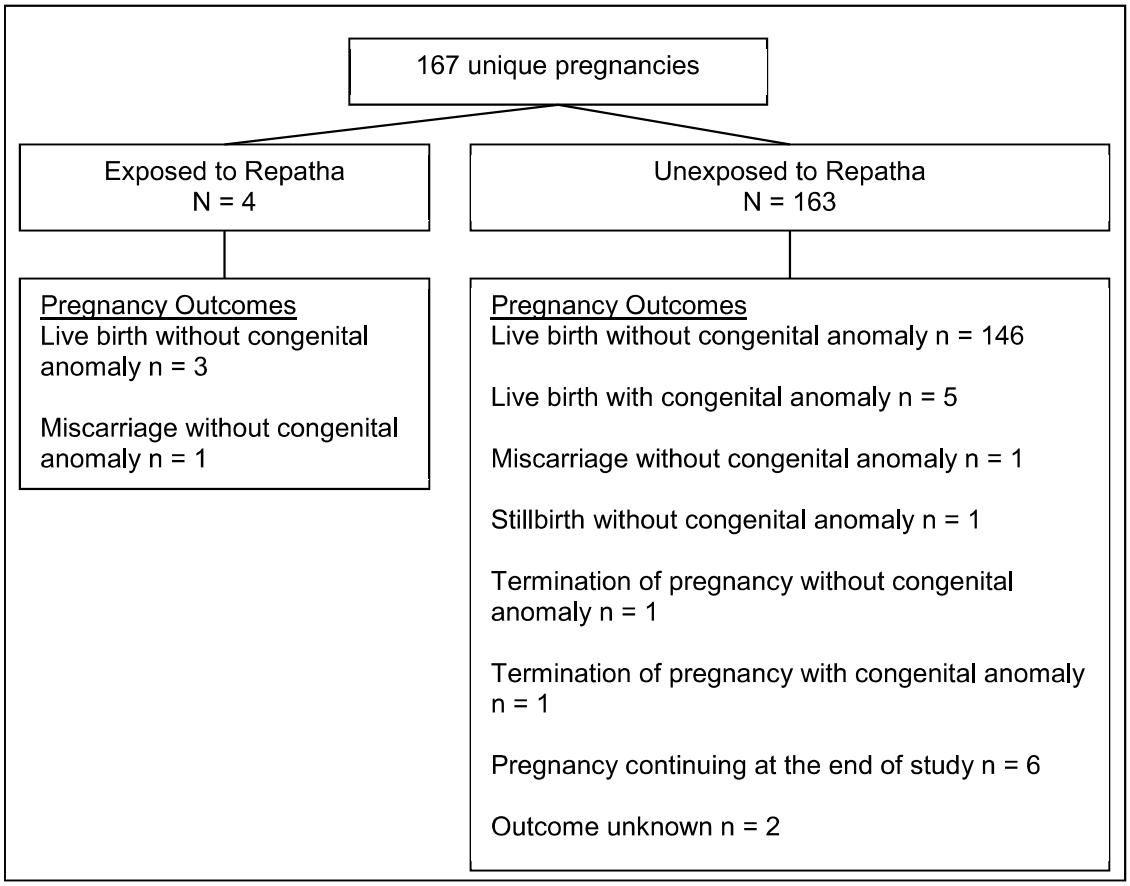
The original data source was patient records from routine follow-up of subjects. Information available for each subject on all variables was reported by study site staff in the study-specific sponsor database.

- **Results**

Thirty-two sites in 14 countries enrolled subjects. At the time of study discontinuation, 167 unique pregnancies were enrolled (5 homozygous FH [HoFH], 154 heterozygous familial hypercholesterolaemia [HeFH], 6 FH type unknown, 2 missing FH type). Of these, 4 pregnancies (2 HoFH and 2 HeFH) were classified as exposed to Repatha and 163 pregnancies were classified as unexposed to Repatha. Pregnancy outcomes are summarized in Figure 1-1.

Among the exposed pregnancies, 1 subject received Repatha during the first trimester and the pregnancy ended in miscarriage without evidence of malformations. The remaining 3 exposed pregnancies received Repatha prior to conception (n = 2) or received Repatha both prior to conception and during the first trimester (n = 1) and all 3 had live births without congenital anomaly. Two infants had no signs of developmental delays at 6 and 12 months; no data is available for the third infant.

Figure 1-1. Summary of Pregnancy Outcomes



- **Discussion**

At the time of study discontinuation, data was available for 167 enrolled pregnancies, of which 4 were classified as exposed to Repatha. Hence, it is not possible to reach any meaningful conclusion on the impact of the study results on the benefit-risk balance of Repatha in women exposed to Repatha during pregnancy/breastfeeding.

- **Marketing Authorization Holder(s)**

Amgen Europe B.V.

- **Names and Affiliations of Principal Investigators**

A list of all collaborating institutions and investigators will be made available upon request.