Summary Table of Study Protocol

Title	GENESIS: AIMOVI**G**® Pr**e**g**n**ancy **E**xpo**s**ure Reg**is**try
Protocol version identifier	Original - Version 1.0
Date of last version of the protocol	Not Applicable
EU Post Authorization Study (PAS) Register No	Unavailable for first version
Active Substance	erenumab-aooe
Medicinal Product	erenumab-aooe (Aimovig®), 70 mg or 140 mg
Product Reference	AMG 334
Procedure Number	BLA 761077
Joint PASS	Yes
Research Question and Objectives	This study will address a requirement by the Food and Drug Administration (FDA) to conduct a prospective observational study of pregnant women exposed to erenumab-aooe to evaluate maternal, fetal, and infant outcomes. Primary Objective • To estimate the proportion of major congenital malformations in infants of women with migraine exposed to erenumab-aooe during pregnancy compared to infants of women with migraine unexposed to erenumab-aooe (internal comparator) Secondary Objectives Secondary objectives include the following: • In women exposed to erenumab-aooe during pregnancy, - To estimate the proportion of pregnancy complications - To estimate the proportion of spontaneous abortion, still birth, elective termination, and preterm birth • In infants of women exposed to erenumab-aooe during pregnancy, - To estimate the proportion of small-for-gestational age - To estimate the proportion of minor congenital malformations - To estimate the proportion of postnatal growth and development deficiency through the first year of life

	• To compare the proportion of maternal, fetal, and infant outcomes of women with migraine exposed to erenumab-aooe consisting of women with migraine who have not been exposed to erenumab-aooe before or during pregnancy (internal comparator) • To compare the frequency of major congenital malformations of women with migraine exposed to erenumab-aooe during pregnancy with women representing the prevalence of birth defects in the general population (external comparator)
Country of Study	United States
Author	PPD PhD Email: PPD PPD , MD, PhD Email: PPD PPD , MD Email: PPD

Marketing Authorization Holder

Marketing authorization holder	Amgen Inc. Thousand Oaks, CA 91320
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Investigator's Agreement

I have read the attached protocol entitled GENESIS: AIMOVIG® Pregnancy Exposure Registry, dated *20 August 2020*, and agree to abide by all provisions set forth therein.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my Subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.

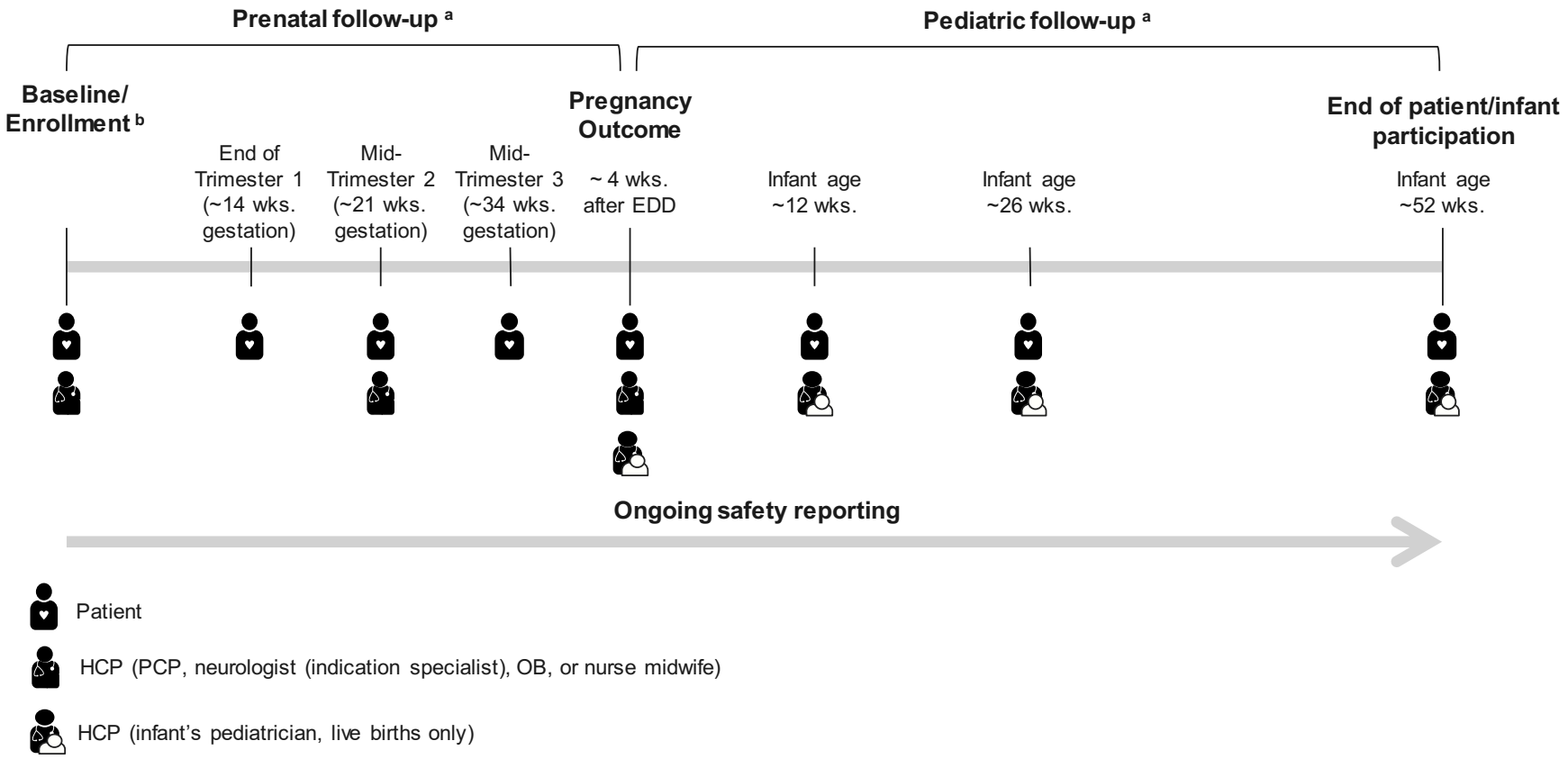
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature
PPD

Name of Investigator

Date (DD Month YYYY)

Study Design Schema



EDD = estimated date of delivery; HCP = healthcare provider; OB = obstetrician; PCP = primary care physician

[a] Timepoints of patient and HCP contact shown are based on expected intervals and may vary based on real-world observational data collection. Patient will be contacted if the HCP is unresponsive. The preferred source of information will be the HCP.

[b] Patients must be enrolled prior to the pregnancy outcome (ie, pregnancy loss or live birth).

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2. List of Abbreviations

Abbreviation	Definition
AE	adverse event
BMI	body mass index
CC	coordinating center
CDC	Centers for Disease Control and Prevention
CGRP	calcitonin gene-related peptide
CI	confidence interval
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
eCRF	electronic case report form
EDC	electronic data capture
EDD	estimated date of delivery
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act of 1996
ICF	informed consent form
ICHD-III	International Classification of Headache Disorders (3rd Edition)
IRB	Institutional Review Board
LAR	legally acceptable representative
LMP	last menstrual period
mAb	monoclonal antibody
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	marketing authorization holder
NSAID	nonsteroidal anti-inflammatory drug
OB	Obstetrician
OR	odds ratio
OTC	over the counter
PAS	post-authorization study
PBRER	periodic benefit-risk evaluation report
PCP	primary care physician
SAE	serious adverse event
SAP	statistical analysis plan
SDV	source data verification
SPR	standardized prevalence ratio
U.S.	United States

3. Responsible Parties

Amgen Inc. is the study Sponsor, responsible for authoring the protocol and regulatory interactions. IQVIA™ (contract research organization [CRO]) is responsible for all operational aspects of the study including data analysis.

4. Abstract

- Study Title: GENESIS: AIMOVI**G**® Pr**e**g**n**ancy **E**xpo**s**ure Reg**is**try
- Study Background and Rationale

  This study will address a requirement by the Food and Drug Administration (FDA) to conduct a prospective observational study of pregnant women exposed to erenumab-aooe (Aimovig®) to evaluate maternal, fetal, and infant outcomes. Maternal, fetal, and infant outcomes of women exposed to erenumab-aooe during pregnancy will be compared with 2 unexposed comparator cohorts: 1) women with migraine who have not been exposed to erenumab-aooe before or during pregnancy (internal comparator); and 2) pregnant women without migraine (external comparator). The registry will identify and record pregnancy complications, major and minor congenital malformations, spontaneous abortions, still births, elective terminations, preterm births, small-for-gestational age births, and any other adverse outcomes.
- Research Question and Objectives
  - Primary Objective: To estimate the proportion of major congenital malformations in infants of women with migraine exposed to erenumab-aooe during pregnancy compared to infants of women with migraine unexposed to erenumab-aooe (internal comparator)
  - Secondary Objectives
    - In women exposed to erenumab-aooe during pregnancy,
      - To estimate the proportion of pregnancy complications
      - To estimate the proportion of spontaneous abortion, still birth, elective termination, and preterm birth
    - In infants of women exposed to erenumab-aooe during pregnancy,
      - To estimate the proportion of small-for-gestational age
      - To estimate the proportion of minor congenital malformations
      - To estimate the proportion of postnatal growth and development deficiency through the first year of life
    - To compare the proportion of maternal, fetal, and infant outcomes of women with migraine exposed to erenumab-aooe of women with migraine who have not been exposed to erenumab-aooe before or during pregnancy (internal comparator)
    - To compare the frequency of major congenital malformations of women with migraine exposed to erenumab-aooe during pregnancy with women representing the prevalence of birth defects in the general population (external comparator)

- Study Design/Type

  This study is a prospective observational registry of pregnant women exposed to erenumab-aooe to evaluate maternal, fetal, and infant outcomes.

- Study Population or Data Resource

  Primary data will be collected from 1421 pregnant women (to observe 749 live births) with migraine in the United States (U.S.) who have been exposed to erenumab-aooe during the 16 weeks prior to their last menstrual period (LMP) or at any time during pregnancy. The frequencies of pregnancy, fetal and infant outcomes will be presented in comparison to both a cohort of pregnant women with migraine who were not exposed to erenumab-aooe (internal comparator, of approximately equal sample size) and external databases of pregnant women without migraine representing the general population (external comparator). The total duration of per patient participation is up to 21 months and the total expected duration of the study is approximately 7 years.

- Summary of Patient Eligibility Criteria

  Inclusion Criteria:

  - Patient consent obtained prior to enrollment
  - Age 18 years or older at the time of signing the informed consent form (ICF)
  - Currently pregnant
  - The outcome of the pregnancy (ie, pregnancy loss or live birth) must not be known
  - Confirmed clinical diagnosis of migraine by evaluation of the patient's treating physician (ie, neurologist, primary care physician [PCP]), categorized into 1 of 2 study cohorts:
    - Erenumab-aooe exposed cohort: Documentation of exposure to erenumab-aooe from 16 weeks prior to LMP or at any point during the patient's pregnancy
    - Internal comparator cohort: Documentation of no exposure to any calcitonin gene-related peptide (CGRP) antagonist from 5 half-lives prior to LMP or at any point during the patient's pregnancy
  - Agrees to sign the Release of Medical Information Form permitting the study to contact her healthcare providers (HCPs) (eg, PCP, neurologist [indication specialist], obstetrician [OB], nurse midwife) and the infant HCP (eg, pediatrician) for medical information

Exclusion Criteria:

- Women currently participating in another investigational device or investigational drug study, currently taking an investigational medicinal product, or having taken an investigational product within 3 months prior to LMP or during pregnancy, Other investigational procedures while participating in this study are excluded.
- Women exposed to any medication in the same pharmacological class as erenumab-aooe (ie, CGRP monoclonal antibody [mAb]) in the period from 5 half-lives prior to LMP through the end of pregnancy.

- Follow-up

  Data will be collected from patients and their HCPs during pregnancy and through 1 year after birth (infant's HCP and/or the patient). Where the HCP is unavailable, the patient can report the necessary information to the study coordinating center (CC) staff for entry into the electronic case report form (eCRF). If information is reported by both the patient and the HCP, the HCP reported data will take precedent.

  Follow-up will cease if the patient is lost to follow-up, consent is withdrawn, death (mother and/or infant), study termination, or the study ends (whichever comes first).

- Variables
  - Outcome Variables

    Primary Outcome:

    - Major congenital malformations classified according to the Metropolitan Atlanta Congenital Defects Program (MACDP) classification system (see Section 9.2.1.1.1. All potential congenital malformations identified by the patient's HCP or the infant's HCP will be evaluated by a committee of at least 3 qualified, independent teratologists, who will be blinded to patient exposure status, using all available medical records.

    Secondary Outcomes:

    - Pregnancy Complications
      - Pre-eclampsia, as diagnosed by the treating HCP; often defined as the presence of hypertension on 2 occasions at least 4 hours apart after 20 weeks gestation (in a woman with a previously normal blood pressure) and proteinuria; or new-onset hypertension accompanied by thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms.
      - Pregnancy-induced hypertension: high blood pressure associated with pregnancy as diagnosed by the treating HCP.
      - Preterm Labor: as diagnosed by the treating HCP; defined by regular contractions of the uterus resulting in changes in the cervix that start before 37 weeks of pregnancy.

- Gestational Diabetes: as diagnosed by the treating HCP; characterized by carbohydrate intolerance with first onset or first recognition during pregnancy; or have a record of a failed oral glucose tolerance test during pregnancy.
- Placenta Previa: as diagnosed by the treating HCP; the patient's cervix is fully or partially covered by baby's placenta.

- Pregnancy Outcomes
  - Elective or Therapeutic Pregnancy Terminations: defined as any induced or voluntary fetal loss during pregnancy.
  - Spontaneous Abortions: defined as loss of a fetus due to natural causes at < 20 weeks of gestation.
  - Fetal Death or Stillbirth: death of a fetus prior to birth at or after 20 weeks of gestation.
  - Preterm Birth: a live birth prior to 37 weeks of gestation (www.cdc.gov). Early preterm (< 34 weeks), late preterm (34 weeks to 36 weeks), early term (37 weeks to 38 weeks) are additional stratifications that may be considered during the analysis.
- Infant Outcomes
  - Minor congenital malformations: classified according to the MACDP classification system (see Section 9.2.1.1.1).
  - Size for Gestational Age: all live births will be classified as small, appropriate, or large for gestational age using the Centers for Disease Control and Prevention (CDC) definition (www.cdc.gov) of birth weight below the 10th percentile, between the 10th and 90th, and above the 90th percentile for age, respectively.
  - Low Birth Weight: an infant with low birth weight will be classified as weighing under 2500 g (www.cdc.gov). Very low birth weight are infants who weigh < 1500 g and moderate birth weight ranges between 1500 g to 2499 g; these are additional stratifications that may be considered during the analysis.
  - Postnatal Growth and Development: developmental milestones (ie, social/emotional, language/communication, cognitive, movement/physical development milestones, as defined by the CDC [CDC 2016]).

- Exposure Variables: The following criteria will be used to assign women to 1 of 2 registry cohorts, as determined by exposure to erenumab-aooe:
  - **Erenumab-aooe exposed cohort**: Documentation of exposure to erenumab-aooe from 16 weeks prior to LMP or at any point during the patient's pregnancy. Erenumab-aooe exposure information will be recorded including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable].
  - **Internal comparator cohort:** Documentation of no exposure to any CGRP mAb from 5 half-lives prior to LMP or at any point during the patient's pregnancy.

Note: the external comparator exposure assessments will not be determined, as patient-level data is not available; these cohort(s) represent the prevalence of birth defects in the general population.

- Other Covariates
  Other key study covariates are described in Section 9.3.3, with specified collection time points at baseline, during pregnancy, at delivery (estimated within 4 weeks of delivery date), during infant follow-up (through 1 year) and at early termination (if applicable).

- Study Sample Size
  To adequately power an internal comparison of the proportion of major congenital malformation events in the erenumab-aooe exposed, and assuming a 15% drop-out rate and a live birth rate of 62% (FDA, 2002), 1421 erenumab-aooe exposed pregnant women with migraine would need to be enrolled to observe 749 live births. This sample size would provide 80% power to detect a risk ratio of 2.0 or greater in major congenital malformations relative to an assumed prevalence of 3% in the internal comparator cohort (CDC, 2008) at a significance level of α=0.05.

- Data Analysis

  The primary outcome of interest for this study is major congenital malformations; other outcomes are classified as secondary. The overall frequency (proportion, 95% confidence interval [CI]) of selected adverse pregnancy outcomes will be calculated, as well as frequencies of specific outcomes, eg, spontaneous abortions, stillbirths, elective or therapeutic terminations, and preterm births. The same will be calculated for selected adverse fetal, neonatal, and infant outcomes at birth and through at least the first year of life of infants (ie, major and minor congenital malformations, small-for gestational age, and postnatal growth and development). The MACDP birth defects classification system will be used to characterize major and minor congenital malformations for this study.

  All analyses will be conducted overall (ever exposed during pregnancy) and by earliest trimester of erenumab-aooe exposure. Data analysis for major congenital malformations will be based on first trimester exposure to erenumab-aooe. The primary data analysis will exclude women who have received first trimester prenatal screening in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected, because these disorders are unrelated to medication use. If sufficient numbers are obtained, analyses will also be

presented by the subgroups of maternal age, race/ethnicity, prior history of elective or therapeutic pregnancy termination status, prenatal screening result (positive versus negative), exposure to migraine medications of special interest at baseline, and other important risk factors. Prevalence of primary and important secondary outcome measures and associated 95% CIs will be calculated by subgroups.

Similar descriptive analyses summarized above will be performed on the internal comparator cohort consisting of pregnant women with migraine who were not exposed to erenumab-aooe. If sufficient numbers are observed, a subgroup analysis will be performed by exposure to other migraine preventive treatments (other than erenumab-aooe).

Outcome frequencies will be described with both the internal comparator cohort and other available background prevalence from external comparator cohort(s). The primary analysis will be adequately powered to detect an a priori clinically meaningful difference in the proportion of major congenital malformations between the erenumab-aooe exposed cohort and the internal unexposed cohort. The comparison of the erenumab-aooe exposed cohort to the internal comparator cohort will be performed using the risk ratio and 95% CIs.

In addition, comparisons may be explored using odds ratios (ORs) adjusted to relevant covariates as applicable, if sufficient number of outcomes are available in the subgroups. Sensitivity analysis for spontaneous abortion as occurring before 22 weeks of gestation, for congenital malformations excluding women with exposure to known or potential teratogenic medications during pregnancy, and other potential sensitivity analyses of interest (if sufficient numbers allow) will be performed.

Existing data from external comparator cohort(s) will be used to compare the prevalence of selected adverse pregnancy events and of selected adverse fetal, neonatal, and infant events at birth and through at least the first year of life of infants in the registry (where available). The MACDP will be the primary external comparator cohort. Reports from The European Surveillance of Congenital Anomalies (EUROCAT) will also be used for supportive evidence and comparisons of outcome prevalence, in addition to other possible external databases as they become available. These comparisons will be based on examinations of point estimates and 95% CIs from each of the sources, and no inductive statistical inferences will be made.

5. Amendments and Updates

None.

6. Milestones

Study milestones are given in Table 1.

Regular study updates will be produced for annual safety reporting requirements. An interim enrollment assessment will be conducted at year 3 of the study and every year thereafter to evaluate patient enrollment and assess study futility, as participation in this registry is anticipated to be low.

Table 1. Study Milestones

Milestone	Planned date
Start of data collection	January 2021
End of data collection	November 2027
Study progress reports	Annually [a]
Interim analysis [b]	November 2024
Registration in the EU PAS register	October 2020
Final report of study results	November 2028

EU = European Union; PAS = post-authorization study
[a] Annual study progress reports to align with scheduled safety reporting requirements, 2021 - 2027.
[b] An interim analysis will be conducted at year 3 of the study to evaluate patient enrollment and estimate sample size for the study.

7. Rationale and Background

7.1 Diseases and Therapeutic Area

Migraine is a neurological disorder characterized by recurrent headache attacks of moderate to severe pain. Migraines affect up to 18% of the female population and 6% of the male population (Lipton et al, 2007). The prevalence of migraine is highest during reproductive age, peaking in middle life (30 to 49 years) (7.9% to 9.0% in men and 25.5% to 28.1% in women) and is lower in children/adolescents and those older than age 60. In a 2010 survey of United States (U.S.) households, 27.5% of women aged 18 to 44 years old reported having a migraine/severe headache in the past 3 months (National Center for Health Statistics, 2012).

Migraine often improves during pregnancy; however, this varies by whether women have migraine with aura. For patients who have migraine without aura, approximately 47% of women will have improvement or remission of migraine in the first trimester, increasing to 83% in the second trimester, and 87% in the third trimester (Sances et al, 2003). Migraine with aura is less likely to improve during pregnancy (Robbins, 2018).

Treatment for migraine includes medications for acute migraine as well as preventive medications. Acute treatments that are commonly used for migraine attacks include triptans, ergots, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), and antiemetic agents individually or in combination (Charles, 2017). The most commonly used therapies for migraine prevention include tricyclic antidepressants (eg, amitriptyline and nortriptyline), beta blockers, anticonvulsants (eg, topiramate and divalproex sodium), and botulinum toxin.

Up to 70% of pregnant women with migraine require a behavioral or a pharmacologic intervention (Contag and Bushnell, 2010). Although nonpharmacologic therapies are recommended for migraine management during pregnancy, acute medications used to treat migraine include acetaminophen and metoclopramide; however, narcotics, NSAIDs (depending on the trimester) and triptans may also be used (Negro et al, 2017; Robbins, 2018).

Preventive medications that may be used during pregnancy include memantine and beta blockers, such as propranolol (Negro et al, 2017; Robbins, 2018). Most beta blockers are generally thought to be safe and are commonly used to treat hypertension in pregnant women, but they may be associated with intrauterine growth restriction. Topiramate and valproic acid should be avoided during pregnancy due to their teratogenic effects (Hernández-Díaz et al, 2012; Negro et al, 2017; Robbins, 2018).

Erenumab-aooe (Aimovig®) was approved by the U.S. Food and Drug Administration (FDA) on 17 May 2018, for the preventive treatment of migraine in adults (AIMOVIG® Prescribing Information). Aimovig® is also approved of in the European Union (EU), Switzerland, and Australia. Erenumab-aooe is a human monoclonal antibody (mAb) that inhibits the receptor for calcitonin gene-related peptide (CGRP) and has demonstrated a favorable safety profile. In 3 randomized, double-blind, placebo-controlled studies of patients who received at least 1 dose of Aimovig® for the preventive treatment of episodic (NCT 02456740, NCT 02483585) or chronic migraines (NCT 02066415), the most common adverse reactions (incidence ≥ 3% and more often than placebo) that occurred during the first 3 months were injection site reactions (such as injection site pain, injection site erythema, and injection site pruritus) and constipation (Goadsby et al, 2017; Tepper et al, 2017; Dodick et al, 2018).

7.2 Rationale

Congenital malformations, structural (eg, cleft lip/palate, heart defects, neural tube defects, heart defects, abnormal limbs) and functional/developmental (eg, sensory problems, metabolic disorders, nervous system problems, degenerative disorders), affect about 3.0 per 100 live births in the U.S. (CDC, 2008) and are the leading cause of infant deaths (about 20% of all infant deaths) (Matthews et al, 2015). The European Surveillance of Congenital Anomalies (EUROCAT) estimated the prevalence of congenital anomalies as 25.6 per 1,000 live births (95% confidence interval [CI] 25.4 to 25.8) from 2012 to 2016 (EUROCAT Website Database, 2018).

It is inconclusive whether pregnant women with migraines have shown an increased risk of adverse pregnancy and infant outcomes. When comparing 777 women suffering from migraine with 182 non-migrainous women in the United Kingdom, the incidence of miscarriage or stillbirth (27% versus 29%) and toxemia (both 18%) were very similar in both groups, and the overall incidence of birth defects were similar (3.36% versus 3.97%) (Wainscott et al, 1978).

Triptans are currently classified as a category C drug. Data from a prospective Pregnancy Registry observing birth defects in 4.2% (95% CI 2.6% to 6.5%) of infants born to women using Sumatriptan during pregnancy (Ephross and Sinclair, 2014), which is consistent with general population birth defect rates. Compared to a non-migraine cohort of German pregnant women, the rates of major birth defects (adjusted odds ratio [OR] 0.84), spontaneous abortions (OR 1.20), preterm delivery (OR 1.01), and preeclampsia (OR 1.33) were not increased in 432 triptan-exposed pregnancies (Spielmann et al, 2018).

In a meta-analysis of publications regarding pregnancy outcomes following prenatal exposure to triptans, no significant increases in pregnancy outcomes rates were observed when comparing the triptan-exposed group with the migraine (no triptans) control group (major congenital malformations, prematurity, or spontaneous abortions) and when comparing the triptan-exposed group with the healthy controls (major congenital malformations) (Marchenko et al, 2015). However, when compared with healthy controls, the triptan-exposed group and the migraine (no triptans) control group had increased rates of spontaneous abortions and major congenital malformations, respectively.

Conversely, a large case-control study of 4911 Taiwanese women with migraine detected an increased risk for low birthweight (adjusted OR 1.16), preterm birth (OR 1.24), preeclampsia (OR 1.34), and cesarean delivery (OR 1.16) when compared with women without migraine (Chen et al, 2010). A population-based study from Hungary found a higher risk of preeclampsia, limb deficiencies, neural tube defects, and poly/syndactyly among women who experienced migraines any time during pregnancy compared with pregnant women without migraines (Bánhidy et al, 2006; Bánhidy et al, 2007). A prospective cohort study of 376 pregnant women in Italy detected an increased incidence of preterm labor in patients with migraine compared with those without migraine (Marozio et al, 2012).

Given almost half of pregnancies are unplanned and anti-migraine medication is frequently used by women of reproductive age (Finer and Zolna, 2011), pregnancy outcomes and fetal exposures should be monitored due to the likelihood of intentional or inadvertent exposure to anti-migraine medications (Honein et al, 1999; Ephross and Sinclair, 2014).

Although erenumab-aooe clinical trials have demonstrated a favorable risk benefit profile, there are no adequate or well-controlled studies on the effects on pregnancy and offspring associated with the use of erenumab-aooe during pregnancy, during lactation, and/or before conception (AIMOVIG® Prescribing Information). In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when pregnant monkeys were administered erenumab-aooe subcutaneous from organogenesis through parturition at exposures up to 16-fold the exposure at the maximum recommended human dose of 140 mg monthly.

This study will address a requirement by the FDA to conduct a prospective, observational study of pregnant women exposed to erenumab-aooe to evaluate maternal, fetal, and infant outcomes of pregnant women exposed to erenumab-aooe.

7.3 Statistical Inference (Estimation)

To meet the primary objective, this study will estimate the proportion of major congenital malformations in the erenumab-aooe exposed cohort and compare to the proportion of major congenital malformations in the unexposed internal comparator using the risk ratio and 95% CI.

8. Research Question and Objectives

8.1 Primary

The primary objective is to estimate the proportion of major congenital malformations in infants of women with migraine exposed to erenumab-aooe during pregnancy compared to infants of women with migraine unexposed to erenumab-aooe (internal comparator).

8.2 Secondary

Secondary objectives include the following:

- In women exposed to erenumab-aooe during pregnancy,
  - To estimate the proportion of pregnancy complications
  - To estimate the proportion of spontaneous abortion, still birth, elective termination, and preterm birth
- In infants of women exposed to erenumab-aooe during pregnancy,
  - To estimate the proportion of small-for-gestational age
  - To estimate the proportion of minor congenital malformations
  - To estimate the proportion of postnatal growth and development deficiency through the first year of life
- To compare the proportion of maternal, fetal, and infant outcomes of women with migraine exposed to erenumab-aooe consisting of women with migraine who have not been exposed to erenumab-aooe before or during pregnancy (internal comparator)
- To compare the frequency of major congenital malformations of women with migraine exposed to erenumab-aooe during pregnancy with women representing the prevalence of birth defects in the general population (external comparator)

9. Research Methods

9.1 Study Design

The design of this pregnancy exposure registry is consistent with relevant guidelines and recommendations (FDA, 2019; European Medicines Agency, 2005; Gliklich et al, 2014; Andrews et al, 2008). This prospective observational registry will collect primary data from pregnant women with migraine and their healthcare providers (HCPs) (eg, primary care physician [PCP], neurologist [indication specialist], obstetrician [OB], nurse midwife or pediatrician) from the U.S. (see Study Design Schema). The coordinating center (CC) is responsible for obtaining informed consent and all patient and HCP contacts during the study. Patients' data obtained via questionnaires administered to patients or their HCPs will be recorded on electronic case report forms (eCRFs) by the CC.

Women who have been exposed to erenumab-aooe during the 16 weeks prior to their last menstrual period (LMP) or at any time during pregnancy are eligible for the

erenumab-aooe-exposed study cohort. The 16-week exposure period prior to LMP accounts for the effective half-life of erenumab-aooe (28 days; AIMOVIG® Prescribing Information), with an additional buffer added. Inclusion of exposures prior to LMP is based on the half-life and standard of care dosing schedule of erenumab-aooe. Dosing and treatment duration of erenumab-aooe as part of this observational study is at the discretion of the HCP in accordance with local clinical practice and local labeling.

The internal comparator cohort (erenumab-aooe-unexposed) will consist of currently pregnant women with clinically confirmed migraine who were not exposed to any CGRP mAb during 5 half-lives prior to their LMP or at any time during pregnancy. Internal comparator cohort patients will be enrolled and follow the same study procedures for follow-up and data collection as the erenumab-aooe exposed cohort.

Major congenital malformations are the primary outcomes of interest for this study, and other pregnancy, maternal, fetal, and infant outcomes are classified as secondary. Data on risk factors, migraine treatment exposures, other therapeutic or environmental exposures, and adverse maternal, fetal, and infant outcomes will be collected from patients and their HCPs during pregnancy and through 1 year after birth (infant's HCP and/or the patient). Major and minor congenital malformations will be classified according to the Metropolitan Atlanta Congenital Defects Program (MACDP) classification system and evaluated by a committee of at least 3 qualified, independent teratologists using all available medical records.

The frequencies of outcomes will be presented in comparison to both existing databases and the internal comparator cohort. The primary analysis will be adequately powered to detect an a priori clinically meaningful difference in the proportion of major congenital malformations between the erenumab-aooe exposed cohort and the internal unexposed cohort.

The study is voluntary and exposure to erenumab-aooe or any other migraine treatment(s) during the study period will be according to national labeling and local standard of care. Any currently pregnant woman with migraine qualifying for either the exposed or comparator cohort, as defined above, will be eligible for the study unless they are participating in another investigational device or investigational drug study, currently taking an investigational medicinal product, or having taken an investigational product within 3 months prior to LMP or during pregnancy. Follow-up will cease if the patient is lost to follow-up, consent is withdrawn, death (mother and/or infant), study termination, or the study ends (whichever comes first). The total duration of per patient

participation is up to 21 months and the total expected duration of the study is approximately 7 years.

An interim analysis at 3 years will be performed to evaluate enrollment and to estimate sample size. Methods to increase registry awareness and enhance patient recruitment and retention are outlined in protocol Section 9.4.4.

9.2 Setting and Study Population

Patients or HCPs can initiate enrollment through the CC. HCPs (eg, PCPs, neurologists [indication specialists], OBs, nurse midwives) who treat patients with migraine including Investigators involved in ongoing or future clinical studies of erenumab-aooe will be informed of the study and asked to refer any patient who becomes pregnant to the study CC. Patients can express interest in enrolling in the Pregnancy Registry by providing contact details on the study website. The CC will contact any potential patients to review consent and initiate enrollment. Future studies involving erenumab-aooe sponsored by Amgen may provide protocol language that describes this Pregnancy Registry study and the process of referring any women who become pregnant. Reporting of pregnancy exposures to erenumab-aooe is voluntary. Awareness will be raised to HCPs that any potentially eligible pregnant patients (either for the exposed or the internal comparator cohort) should be referred to the registry as early as possible; ideally before prenatal testing has been performed. Pregnancies with known outcomes (ie, pregnancy loss or live birth) at the time of the initial report will not be included in the study but will be followed by Amgen according to standard post-marketing pharmacovigilance.

9.2.1 Study Population

Currently pregnant women with clinically confirmed migraine in the U.S. who have been exposed to erenumab-aooe during the 3 months prior to their LMP or at any time during pregnancy will be considered for inclusion in the exposed study cohort. An internal comparator cohort will consist of currently pregnant women with clinically confirmed migraine who have not been exposed to any CGRP mAb, while secondary data sources will be used to compare results to external comparator cohort(s) representing the prevalence of birth defects in the general population (see Section 9.2.4 Patient Eligibility).

Women will be enrolled prospectively and may be enrolled from the post marketing setting or other clinical or observational studies of erenumab-aooe, unless prohibited by exclusion criteria noted in Section 9.2.4.2. To reduce bias that may occur if outcome information is known prior to enrollment, women should be enrolled in the study as soon

as their pregnancy is known, preferably prior to any informative prenatal testing (where the knowledge of the primary study outcome of the pregnancy would be known – either normal or abnormal), and preferably in the first trimester before 20 weeks gestation. Women who receive any first trimester prenatal screening after enrollment (post-enrollment) will be included in the primary analysis. Decision criteria with regards to prenatal testing before enrollment (pre-enrollment) will be applied to the study population for inclusion into the primary analysis and is outlined in Section 9.7.1.2. Table 2 are the pertinent descriptions.

Table 2. Timing and Results of Prenatal Screening Tests: Key Descriptions

Groups Determined by Test and Result	Inclusion in Analyses
Pre-enrollment prenatal screening: women who have already received prenatal testing where the result is known prior to enrollment	Variable based on subgroup
Subgroup 1: Women who have all normal findings	Included in primary analysis; included in sensitivity analysis of known test result(s) prior to enrollment
Subgroup 2: Women who have pregnancies with aneuploid disorders or genetic disorders that cause major congenital malformations	Excluded from primary and secondary analysis; analyzed as a separate group
Subgroup 3: Women who have pregnancies with results (normal or abnormal) that are unrelated to aneuploid disorders or genetic disorders that cause major congenital malformations	Included in primary analysis; included in sensitivity analysis of known test result(s) prior to enrollment
Women who had no prenatal screening prior to enrollment in the registry	Included in primary analysis; exclude aneuploid or genetic disorders
Women who had prenatal screening after enrollment in the registry	Included in primary analysis; excluded in primary analysis women who have pregnancies with aneuploid disorders or genetic disorders that cause major congenital malformations

9.2.1.1 External Comparator Cohorts

External comparators can provide additional context for study results, and will be used to descriptively characterize study results, with MACDP reports serving as the primary external comparator; representing the estimated underlying prevalence of major structural or genetic birth defects in the general U.S. population. Only aggregate, population-level data or published reports would be used for comparison. Further details of external comparator cohort analysis are in Section 9.7.2.5.2.

9.2.1.1.1 Metropolitan Atlanta Congenital Defects Program (MACDP)

The MACDP, a population-based tracking system for birth defects, was established in 1967 as the first population-based system for the active collection of information about birth defects in the U.S. (MACDP, 2016). Currently, the MACDP tracking system captures approximately 35,000 births per year from 3 large metropolitan counties in the Atlanta area (5 counties were captured in earlier years). MACDP has monitored trends in birth defects rates and has served as a case registry for descriptive, risk factor, and prognostic studies of birth defects. Since 1998, MACDP surveillance has required that any signs or symptoms of a defect in the child be reported before their sixth birthday. In a 2007 report, the MACDP presented data on the prevalence and descriptive characteristics of birth defects, including 67 individual defects, in metropolitan Atlanta, Georgia, from 1968 to 2003 (Correa et al, 2007).

The frequency of birth defects is measured as prevalence at birth, expressed as the number of affected infants per 1,000 live births. Major structural or genetic birth defects affected approximately 3% of births in the U.S. (CDC, 2008). The prevalence estimates of stillbirth in 2006 and 2008 using MACDP data were 8.0 and 7.6 per 1000 live births plus stillbirths (95% CIs: 7.3, 8.7, and 6.9, 8.4), respectively (Duke and Gilboa, 2014).

9.2.1.1.2 European Surveillance of Congenital Anomalies (EUROCAT)

EUROCAT is a European network of population-based registries for the epidemiologic surveillance of congenital anomalies (EUROCAT, 2017). Started in 1979, the registry includes over 1.7 million births surveyed annually in Europe from 43 registries in 23 countries. Approximately 29% of the European birth population is covered by this network. These population-based registries facilitate the early warning of new teratogenic exposures, evaluate the effectiveness of primary prevention measures, and assess the impact of developments in prenatal screening.

Using 13 registries from the EUROCAT network from 01 January 1998 through 31 December 2011, Groen et al. reported an overall prevalence of congenital anomaly of 27.3 per 1000 births (range, 19.1–39.3 per 1000 births) (Groen et al, 2017). Of the 84,387 pregnancies with a known outcome (99.4%), 2.33% pregnancies were stillbirths, the proportion of early neonatal mortality (within 7 days of birth) was 2.37% and the proportion of late neonatal mortality (between 7 days to 27 days of life) was 0.84%.

9.2.1.1.3 Other Potential Sources

At the time of final report generation, any existing publicly available data sources (registries, cohorts) or published study results pertaining to migraine treatment exposures during pregnancy will be reviewed and considered for a summary of comparisons to results in this registry, where feasible. For example, results from the Sumatriptan, Naratriptan, and Treximet Pregnancy Registry may be a suitable external reference population for the internal comparator cohort (Ephross and Sinclair, 2014). No statistical comparisons will be made.

9.2.2 Study Period

The study start date will be the date of the first data collection: the date from which information on the first study patient is recorded in the study database. The end of the study will be the date from which the last data collected from the last patient is recorded in the study database. The total duration of per patient participation is up to 21 months and the total expected duration of the study is approximately 7 years.

9.2.3 Coordinating Center

This study will be conducted in the U.S. There will be at least 1 CC that is responsible for obtaining informed consent and all patient and HCP contacts during the study. See Figure 1 (Data Flow Overview) for more information on CC data responsibilities.

9.2.4 Patient Eligibility

Women will be screened for eligibility criteria for each pregnancy, should they contribute more than one pregnancy in the Registry. Any within-patient pregnancy correlations will be accommodated in the analysis as part of the statistical analysis plan (SAP).

9.2.4.1 Inclusion Criteria

- Patient consent obtained prior to enrollment
- Age 18 years or older at the time of signing the informed consent form (ICF)
- Currently pregnant
- The outcome of the pregnancy (ie, pregnancy loss or live birth) must not be known
- Confirmed clinical diagnosis of migraine by evaluation of the patient's treating physician (ie, neurologist, PCP), falling into 1 of 2 cohorts:
  - Erenumab-aooe exposed cohort: Documentation of exposure to erenumab-aooe from 3 months prior to LMP or at any point during the patient's pregnancy. Erenumab-aooe exposure information will be recorded including start and stop dates, dose, dosing frequency, reason for discontinuation (if applicable).
  - Internal comparator cohort: Documentation of no exposure to any CGRP mAb from 5 half-lives prior to LMP or at any point during the patient's pregnancy. Agrees to sign the Release of Medical Information Form permitting the study to

contact her HCPs (eg, PCP, neurologist [indication specialist], OB, nurse midwife) and the infant HCP (eg, pediatrician) for medical information

9.2.4.2 Exclusion Criteria

- Women currently participating in another investigational device or investigational drug study, currently taking an investigational medicinal product, or having taken an investigational product within 3 months prior to LMP or during pregnancy. Other investigational procedures while participating in this study are excluded.
- Women exposed to any medication in the same pharmacological class as erenumab-aooe (ie, CGRP mAb) in the period from 5 half-lives prior to LMP through the end of pregnancy

9.2.5 Matching

Matching is currently not planned, but if sufficient sample size allows, propensity score matching may be explored (Section 9.7.2.5.1).

9.2.6 Data Collection

The reporter of information can be the patient, patient's HCP, or infant's HCP where applicable (see Study Design Schema). "Information" includes all variables described in Section 9.3. Where the HCP is unavailable, the patient can report the necessary information to the study CC staff for entry into the eCRF. Where information is reported in duplicate and there is a discrepancy, the HCP reported information will take precedent. Migraine diagnostic and treatment information should be collected and/or confirmed by the treating migraine specialist (neurologist) or PCP (ie, preferably not the OB, nurse midwife, or patient). However, the patient is considered a suitable source for reporting some migraine history characteristics, including their average monthly migraine days and age at migraine onset. Any reported outcome of a major or minor congenital malformation will be adjudicated.

9.2.7 Baseline Period

The baseline period is defined as the first date of data collection after patient informed consent has been signed. Data collected for baseline assessments will be a specific time point consistently for all enrolled patients (eg, the baseline data collection period for current pregnancy information will be defined as at the time since LMP, while co-medication use will examine all available medications classified as current or prior use starting from 3 months prior to LMP). Baseline information will be collected to confirm patient eligibility, collect relevant medical history, and characterize the current pregnancy status of the patient. The following covariates will be collected:

- Documentation of informed consent
- Reporter of information (eg, patient, PCP, OB, neurologist [indication specialist], nurse midwife, other)

- Inclusion/exclusion criteria
- Patient demographics and characteristics (eg, age of mother, education level, race/ethnicity, height, pre-pregnancy and current pregnancy weight)
- Lifestyle risk factors (eg, smoking, caffeine consumption, alcohol use, illicit drug use)
- Current pregnancy information (eg, LMP, gestational age at enrollment, estimated date of delivery [EDD], date and results of any prenatal tests, date and results of any pregnancy complications)
- Medical history:
  - Pregnancy history (eg, parity, gravidity, previous preterm births, previous spontaneous abortions or elective or therapeutic terminations, reason for any elective or therapeutic termination, history of congenital malformations)
  - Medical history and comorbid conditions: surgical and medical history/significant maternal medical conditions other than migraine (eg, diabetes, high blood pressure)
  - Migraine history including: average monthly migraine days before pregnancy, number and duration of migraines and migraine days in the past month (patient-reported), age at migraine onset, type(s) of migraine (chronic, episodic), presence of aura, age at migraine onset, number of prior preventive migraine treatment failures (pre-pregnancy), days of acute migraine treatments each month (pre-pregnancy and by trimester), impact of pregnancy on the intensity of headache
    - If diagnosed with chronic migraine, age at chronic migraine onset
  - Family reproductive history (eg, multiple births, pregnancy complications [ie, preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa], congenital malformations, spontaneous abortions, premature births, chromosomal anomalies, evidence of developmental delays)
- Erenumab-aooe treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Current and prior medication use starting from 3 months prior to LMP through pregnancy including presence of any other prescription migraine treatments, other over the counter (OTC) migraine treatment(s), folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities; including start and stop dates (if applicable)
- Patient adverse events (AEs) and serious adverse events (SAEs) (including event, start date, ongoing or end date, seriousness, severity, relationship to erenumab-aooe, outcome, action taken)

9.2.8 Study Follow-up

Women will be followed from enrollment through the end of their pregnancy and infants will be followed through 1 year after birth. Specific data to be collected during different periods during the follow-up are detailed below. Safety reporting will be ongoing throughout the duration of the study.

During Follow-up of Pregnancy (estimated at 14, 21 and 34 weeks gestation)

- Date of contact
- Reporter of information (eg, patient, PCP, OB, neurologist [indication specialist], nurse midwife, other)
- Current weight
- Changes in lifestyle risk factors (eg, smoking, caffeine consumption, alcohol use, illicit drug use)
- Number of migraines since last follow-up; frequency and duration, with or without aura, number of migraines requiring treatment, any prescription migraine treatments, and days of acute migraine treatments each month (by trimester)
- Changes in comorbid conditions
- Erenumab-aooe treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Current medications, including start and stop dates (eg, any other OTC migraine treatment(s), folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities)
- Pregnancy status, if applicable:
  - Gestational age at contact
  - Any prenatal testing performed and results (eg, rubella titer, toxoplasmosis, venereal disease research laboratory test, hepatitis screen, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein screen, glucose screen)
  - Pregnancy outcome (eg, live births, spontaneous abortions, stillbirths, elective or therapeutic terminations, reason for elective or therapeutic termination [eg, prenatal testing finding, risk to mother's health, undesired pregnancy], and autopsy results and pathology reports, if available)
  - Congenital malformations noted (including description and attribution)
- Patient AEs and SAEs (including event, start date, ongoing or end date, seriousness, severity, relationship to erenumab-aooe, outcome, action taken)

At Delivery (estimated within 4 weeks of delivery date)

- Reporter of information (eg, patient, PCP, OB, neurologist [indication specialist], nurse midwife, infant HCP, other)
- Pregnancy outcome (eg, live birth, stillbirth, spontaneous abortion, elective or therapeutic termination)
- Reason for elective or therapeutic termination (eg, prenatal testing finding, risk to mother's health, undesired pregnancy), if applicable
- Autopsy results and pathology reports, if available
- Mode of birth (vaginal delivery, assisted delivery/cesarean section, type of anesthesia)
- Number of migraines since last follow-up; number of migraines requiring treatment, and any prescription migraine treatments
- Changes in comorbid conditions

- Erenumab-aooe treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Current medications, including start and stop dates (eg, any other OTC migraine treatment(s), folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities)
- Changes in lifestyle risk factors (eg, smoking, caffeine consumption, alcohol use, illicit drug use)
- Patient AEs and SAEs (including event, start date, ongoing or end date, seriousness, severity, relationship to erenumab-aooe, outcome, action taken)
- Infant characteristics:
  - Gestational age at birth
  - Sex
  - Birth weight
  - Length
  - Head circumference
  - Birth order (for multiple births), and number of fetuses
  - Apgar scores (1, 5, and 10 minutes)
  - Congenital malformations noted (including description and attribution)
  - Vaccination information
  - Whether infant is breastfed
  - Infant medication(s)
  - Infant AEs and SAEs (including event, start date, ongoing or end date, seriousness, severity, relationship to erenumab-aooe, outcome, action taken)

Infant Follow-up (estimated at 12, 26 and 52 weeks of age)

- Reporter of information (eg, patient, PCP, OB, neurologist [indication specialist], nurse midwife, infant HCP, other)
- Feeding behavior (including breastfeeding)
- Weight
- Length
- Head circumference
- Postnatal growth and development (ie, social/emotional, language/communication, neurocognitive, movement/physical development milestones)
- Breastfeeding status
- Evidence of any new congenital malformations and growth alterations since last follow-up
- Vaccination information
- Patient and infant AEs and SAEs (including event, start date, ongoing or end date, seriousness, severity, relationship to erenumab-aooe, outcome, action taken)

Early termination of study participation contact, if applicable:

- Reporter of information (eg, patient, PCP, OB, neurologist [indication specialist], nurse midwife, other)
- Assessments appropriate for the time of withdrawal
  - Pregnancy status (eg, gestational age at contact, any prenatal testing performed and results)
  - Pregnancy outcome (eg, live births, spontaneous abortions, stillbirths, elective or therapeutic terminations, reason for elective or therapeutic termination [eg, prenatal testing finding, risk to mother's health, undesired pregnancy], mode of birth, and autopsy results and pathology reports, if available)
  - Infant characteristics (eg, postnatal growth and development, feeding behavior, weight, length, head circumference, breastfeeding status, vaccine information, current medications)
  - Evidence of any new congenital malformations and growth alterations since the last follow-up
  - Patient and infant AEs and SAEs (including event, start date, ongoing or end date, seriousness, severity, relationship to erenumab-aooe, outcome, action taken)
- Termination status
  - Completion of follow-up
  - Early termination/withdrawal (including date of withdrawal, reason for withdrawal)
- Erenumab-aooe treatment, current medications, pregnancy status, and infant characteristics (for live births), and safety events will be collected similarly as during study follow-up.

9.3 Variables

The reporter of variable information can be the patient, patient's HCP, or infant's HCP where applicable (see Section 9.2.6). Appendix F provides a summary table of data collection elements.

9.3.1 Exposure Assessment

The following criteria will be used to assign women to 1 of 2 cohorts, as determined by exposure to erenumab-aooe:

- **Erenumab-aooe Exposed Cohort:** Documentation of exposure to erenumab-aooe from 16 weeks prior (to allow for the half-life of erenumab-aooe) to LMP or at any point during the patient's pregnancy. Exposure information recorded will include start and stop dates, dose, dosing frequency, reason for discontinuation (if applicable).
- **Internal Comparator Cohort:** Documentation of no exposure to any CGRP mAb from 5 half-lives prior to LMP or at any point during the patient's pregnancy. Note: exposure assessments will not be determined for the external comparator cohort(s), as patient-level data is not available; these cohort(s) represent the prevalence of birth defects in the general population.

9.3.2 Outcome Assessment

As shown in Table 3, all outcomes defined in this section will be assessed in both the erenumab-aooe exposed and internal comparator cohorts, as patient-level data will be collected prospectively. The outcome of major congenital malformations will be compared to the prevalence reported for the external comparator population that provides aggregate data, only (MACDP).

Table 3. Summary Key Outcome Assessments Across Data Sources

	Erenumab-aooe Exposed	Internal Comparator	MACDP [a]
Primary Outcome			
Major congenital malformations	X	X	X
Secondary Outcomes			
Pregnancy complications: preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa	X	X	
Pregnancy outcomes: elective or spontaneous termination, fetal death, preterm birth	X	X	
Infant outcomes: minor congenital malformations, size for gestational age, low birth weight, postnatal growth and development	X	X	

MACDP = Metropolitan Atlanta Congenital Defects Program
[a] Additional external comparator data sources may be used (see Section 9.2.1.1), but similar to MACDP, only aggregate data will be available for comparison to this registry.

9.3.2.1 Primary Outcome

9.3.2.1.1 Major Congenital Malformations

Congenital malformations will be classified according to the MACDP classification system (MACDP, 2016) (see Section 9.2.1.1.1) and adjudicated major congenital malformations will serve as the primary outcome in this study (minor malformations will be excluded from the primary analysis). The MACDP classification lists major and minor birth defects that are tracked by MACDP, as well as conditions that are never included and those that are included only under certain circumstances. The code is based on the International Classification of Diseases, 9th Revision, Clinical Modification and the British Pediatric Association Classification of Diseases.

All potential major congenital malformations identified by the patient's HCP or the infant's HCP will be evaluated by a qualified, independent committee of at least

3 teratologists using all available medical records (see Section 9.8.4). The classification of potential major congenital malformations will be based upon the teratologists' adjudication, who will be blinded to patient exposure status. The adjudication process will involve the classification of congenital anomalies by both MACDP and EUROCAT classification systems. In the event any European data sources become available for descriptive comparison to this registry, the EUROCAT classification would be implemented to ensure comparability. However, this is not currently planned.

9.3.2.2 Secondary Outcomes

9.3.2.2.1 Pregnancy Complications

9.3.2.2.1.1 Preeclampsia

Primary preeclampsia will be based on HCP reported diagnosis. It is often defined as the presence of hypertension on 2 occasions at least 4 hours apart after 20 weeks gestation (in a woman with a previously normal blood pressure) and proteinuria; or in the absence of proteinuria, a new-onset hypertension accompanied by 1 of the following conditions: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or cerebral or visual symptoms (ACOG, 2019).

9.3.2.2.1.2 Pregnancy-Induced Hypertension

High blood pressure (elevated: systolic between 120-129 and diastolic less than 80 mg Hg; Stage 1 hypertension: systolic between 130–139 or diastolic between 80–89 mm Hg; Stage 2 hypertension: systolic at least 140 or diastolic at least 90 mm Hg) associated with pregnancy, as diagnosed by the treating HCP (ACOG, 2019).

9.3.2.2.1.3 Preterm Labor

Preterm labor will be based on HCP reported diagnosis. It is often as regular contractions of the uterus resulting in changes in the cervix that start before 37 weeks of pregnancy. Any interventions or treatments provided to the patient as a result of preterm labor will be collected.

9.3.2.2.1.4 Gestational Diabetes

Gestational diabetes will be based on HCP reported diagnosis. It is often characterized by the development of carbohydrate intolerance with first onset or first recognition during pregnancy; a record of an oral glucose tolerance test during pregnancy will also be accepted for data collection, where available (ACOG, 2018).

9.3.2.2.1.5 Placenta Previa

Physician-diagnosed placenta previa: when the baby's placenta fully or partially covers the mother's cervix.

9.3.2.2.2 Pregnancy Outcomes

9.3.2.2.2.1 Elective or Therapeutic Pregnancy Terminations

Elective or therapeutic pregnancy terminations are defined as any induced or voluntary fetal loss during pregnancy. If available, data from pathologic examination of the abortus or fetus will be evaluated by the adjudication committee (see Section 9.8.4) for structural and chromosomal defects. The reason for elective or therapeutic termination will be collected. Elective versus therapeutic terminations will be summarized separately.

9.3.2.2.2.2 Spontaneous Abortions

A spontaneous abortion is defined as loss of a fetus due to natural causes at < 20 weeks of gestation. If available, information from gross or pathologic examination of the abortus or fetus will be evaluated by the adjudication committee (see Section 9.8.4) for structural and chromosomal defects.

9.3.2.2.2.3 Fetal Death or Stillbirth

Fetal death or stillbirth refers to the death of a fetus prior to birth at or after 20 weeks of gestation. In the event of a stillbirth or fetal death, full pathology details will be requested and examined for structural or chromosomal defects. The final classification between fetal death/stillbirth and spontaneous abortion will be based on gestational age.

9.3.2.2.2.4 Live Birth

A live birth refers to a complete expulsion or extraction from its mother of a surviving neonate.

9.3.2.2.2.5 Preterm Birth

A live birth will be classified as preterm prior to 37 weeks of gestation (www.cdc.gov). Preterm birth will be categorized as early preterm (< 34 weeks), late preterm (34 weeks to 36 weeks), and early term (37 weeks to 38 weeks).

9.3.2.2.3 Infant Outcomes

9.3.2.2.3.1 Minor Congenital Malformations

Congenital malformations will be classified according to the MACDP classification system (see Section 9.2.1.1.1) and minor congenital malformations are part of the secondary objectives for this study. All potential minor congenital malformations will be evaluated by at least 3 qualified, independent teratologists using all available medical

records (see Section 9.8.4). The classification of potential minor congenital malformations will be based upon the teratologists' adjudication, who will be blinded to patient exposure status. Adjudicated minor congenital malformations will not be included in the analysis of the primary objective.

9.3.2.2.3.2 Size for Gestational Age

All live births will be classified as small, appropriate, or large for gestational age using the Centers for Disease Control and Prevention (CDC) definition (www.cdc.gov) of birth weight below the 10th percentile, between the 10th and 90th, and above the 90th percentile for age, respectively.

9.3.2.2.3.3 Low Birth Weight

An infant with low birth weight will be classified as weighing under 2500 g (www.cdc.gov). Low birth weight can be subclassified into very low birth weight (< 1500 g) and moderate low birth weight (1500 g to 2499 g).

9.3.2.2.3.4 Postnatal Growth and Development

Domains of developmental milestones (ie, social/emotional, language/communication, neurocognitive, movement/physical development milestones) by age will be defined by guidelines provided by the CDC (CDC 2019). As recommended by the CDC, the World Health Organization Growth Charts (suitable for use in the U.S. from birth to 24 months) will be applied for this study, where infant growth measurements will be used to estimate gender-specific weight-for-length, head circumference-for-age, length-for-age, and weight-for-age percentiles. Developmental milestones will be collected as part of routine clinical practice with pediatrician-determined results of infant status (ie, below, above, or at age appropriate achievement) in each of the domains listed above. "Ages and Stages" or similar standardized assessments may be collected for this study if performed as part of routine clinical care – no additional information will be mandated for collection as part of this study.

9.3.3 Covariate Assessment

9.3.3.1 Baseline Covariates

- Patient demographics and characteristics:
  - Age of patient (mother) at the time of enrollment
  - Education level (Doctoral or professional degree, Master's degree, Bachelor's degree, Associate degree, Postsecondary nondegree award, some college, no degree, High school diploma or equivalent, No formal educational credential)
  - Race (American Indian or Alaska Native, Asian, Black or African American, Hawaiian or Other Pacific Islander, White, Other/Unspecified)

  - Ethnicity (Hispanic or Latino and Not Hispanic or Latino)
  - Height (cm or in)
  - Weight (kg or lbs.); pre-pregnancy and current weight
  - Body mass index (BMI) (derived from height and current weight)
- Lifestyle risk factors
  - Smoking (current, former, never)
  - Caffeine consumption (Y/N)
  - Alcohol use (Y/N; if Y, drinks per week)
  - Illicit drug use (Y/N)
- Current pregnancy information (calendar provided to help recall)
  - Date of LMP
  - Gestational age at the time of enrollment visit
  - EDD
  - Date and results of any prenatal tests
  - Pregnancy complications (ie, physician reported preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa)
  - Pregnancy history
    - Parity: number of pregnancies carried to a viable gestational age (> 20 weeks)
    - Gravidity: number of pregnancies
    - Previous preterm births (for definition, see Section 9.3.2.2.2)
    - Previous spontaneous abortions (for definition, see Section 9.3.2.2.2)
    - Previous elective or therapeutic terminations (for definition, see Section 9.3.2.2.2)
    - Reason for any elective or therapeutic termination,
    - History of congenital malformations
    - Other (specify)
- Surgical and medical history or significant maternal medical conditions other than migraine (eg, diabetes, high blood pressure)
- Migraine history, including type(s) of migraine (chronic, episodic), presence of aura, age at migraine onset, number and duration of migraines and migraine days in the past month (patient-reported), average monthly migraine days prior to pregnancy, number of prior preventive migraine treatment failures (pre-pregnancy), days of acute migraine treatments each month (pre-pregnancy and by trimester), impact of pregnancy on the intensity of headache
  - If diagnosed with chronic migraine, age at chronic migraine onset

- Family reproductive history, including:
  - Multiple births
  - Pregnancy complications (ie, preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa)
  - Congenital malformations
  - Spontaneous abortions
  - Preterm births
  - Chromosomal anomalies
  - Evidence of developmental delays
- Erenumab-aooe treatment (including start and stop dates, dose, dosing frequency, reason for discontinuation [if applicable])
- Current and prior medication use starting from 3 months prior to LMP (including all prescription and any other OTC migraine treatment(s), folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities); including start and stop dates (if applicable)
- Patient AEs and SAEs (including event, start date, ongoing or end date, seriousness, severity, relationship to erenumab-aooe, outcome, action taken)

9.3.3.2 Covariates During Follow-up

Covariates to be collected during pregnancy, at delivery, during infant follow-up and at early termination of study participation (if applicable) are described in Section 9.2.8.

9.3.4 Validity and Reliability

Data will be collected from the patient's HCP or directly from the patient and entered into the eCRF by trained CC staff (see Section 9.4). Standard definitions for the classification of pregnancy outcomes have been used and proper citations have been provided, where applicable. Some outcomes, such as pregnancy complications, will rely on the report of a diagnosis (eg, hypertension) and not individual measurements (eg, systolic and diastolic blood pressure values). Reliability of the data is subject to what is reported by the HCP and/or patient, and methods to ensure the quality of the data to the extent possible is provided in Section 9.6.1. Published literature can be used for comparison of the distribution and/or frequencies of key covariates.

The primary outcome of major congenital malformations and the secondary outcome of minor congenital malformations will be defined using the standard classifications provided by MACDP, with an independent review by a committee of teratologists who will be blinded to the patient's exposure status (see Section 9.8.4).

9.4 Data Sources

9.4.1 Collection of Data on the Electronic Case Report Form

Patients' data obtained via questionnaires administered to patients or their HCPs will be recorded on eCRFs by the CC. The degree of detail and completeness of data collected is dependent on local clinical practice.

9.4.2 Data Collected During the Observation Period

The CC is responsible for patient enrollment (ie, determining eligibility and obtaining informed consent and permission for medical form release) and obtaining all patient and HCP contacts. After a patient provides consent, the CC will obtain demographic and contact information in addition to baseline information at the time of enrollment. All patient and HCP contact information will be confidential and will remain at the CC. Infant HCP contact information will be obtained at the delivery follow-up (estimated within 4 weeks of delivery date). The CC will then contact the patient each trimester to update contact information and ascertain the occurrence of pregnancy outcomes or other events (see Section 9.3 for list of variables). Below is a list of the expected contact points for data collection with patients and HCPs:

Expected contacts with patient:

- Enrollment
- End of Trimester 1 (approximately 14 gestational weeks)
- Mid-Trimester 2 (approximately 21 gestational weeks)
- Mid-Trimester 3 (approximately 34 gestational weeks)
- EDD plus 4 weeks
- Birth plus 12 weeks, 26 weeks, and 52 weeks (live births only)

Expected contacts with the patient's HCP (eg, PCP, neurologist [indication specialist], OB, nurse midwife):

- Enrollment
- Mid-Trimester 2 (approximately 21 gestational weeks)
- EDD plus 4 weeks

Expected contacts with the infant's HCP (eg, pediatrician) (live births only):

- EDD plus 4 weeks
- Birth plus 12 weeks
- Birth plus 26 weeks
- Birth plus 52 weeks

After a patient is enrolled, there will be at least 3 attempts made to contact the patient and/or the HCP via phone, email, fax, and mail, as appropriate, approximately 10 business days apart. If data is obtained after a follow-up interval is passed, the CC will accept and enter the data and continue follow-up of the patient. If an HCP is not responsive at the time points described above, the patient will be asked to provide the information contained on the HCP questionnaires administered by the CC for eCRF entry. If the HCP then responds to contact, their information will supersede the patient-reported information. At all time points, the type of reporter (patient, PCP, neurologist [indication specialist], OB, nurse midwife or pediatrician) will be recorded.

In the routine care setting, patients are seen regularly by their treating physicians either for treatment or for regular assessment after treatment. Thus, no study-specific visits or evaluations are required by this protocol.

If the patient experiences an adverse pregnancy outcome or has an elective or therapeutic termination or a termination of unknown cause, the HCP and patient will be encouraged to report the outcome to the CC as soon as possible. In the event of an elective or therapeutic termination, spontaneous abortion, fetal death or stillbirth, communications with the patients will cease after pregnancy outcome information has been obtained. Amgen Safety will follow-up on all SAEs, including information about fetal or maternal death, with the patient's HCP.

9.4.3 Loss to Follow-up

For study purposes, patients will be considered lost to follow-up if any time-based assessment is missed and the corresponding data have not been received by the CC after making additional follow-up attempts using all contact methods available (eg, phone, fax, registered letter). At least 3 attempts will be made up to 4 months after the expected date of the missed assessment. The patient will be re-opened if additional information is later obtained. All HCPs and secondary contacts will also be contacted prior to considering a patient lost to follow-up. All data collected prior to the patient being lost to follow-up will be used for analyses, if possible. For analysis purposes, the date of study discontinuation will be recorded as the date of last contact.

Registry awareness, recruitment, and retention strategies to maximize enrollment and minimize loss to follow-up are described in Section 9.4.4.

9.4.4 Registry Awareness, Recruitment, and Retention

9.4.4.1 Registry Awareness

The registry will utilize awareness strategies that have appeared to be effective in other pregnancy exposure registry programs. Increased awareness of the registry will use multiple approaches aimed towards both HCPs and patients, such as social media, paper and electronic media, and scientific conferences. The registry will also be included in labeling and listed on the FDA Office of Women's Health Pregnancy Registry website. Registry awareness activities and content will be evaluated on a regular basis to ensure target populations are being reached yet minimize any burden on the recipients. Channels for providing feedback on Registry material and corresponding with potential HCPs and patients will be detailed in a Recruitment and Retention Plan.

9.4.4.2 Registry Recruitment

Active outreach will occur to obtain reports of women with migraine who are exposed to erenumab-aooe during pregnancy, as well as women with migraine who may be eligible for the internal comparator cohort who receive medical care from the same clinical sites. Outreach efforts may include the following:

- Discussion of the Registry with Investigators participating in erenumab-aooe clinical studies, with periodic written reminders
- Collaboration with Investigators of independent migraine registries
- Notification of the Registry to neurologists and other practitioners who may prescribe erenumab-aooe, as well as migraine education and support groups, via the following:
  - Investigator awareness electronic flyer
  - HCP introduction letters
- Collection of patient referral information at enrollment (eg, HCP, website/internet, sponsor, etc.)

Recruitment of patients is dependent on several factors. Uptake of new medications such as erenumab-aooe is unpredictable and has the potential to impact the feasibility of meeting the recruitment targets in the U.S. In addition, the expected pace of exposure to pregnant women and the willingness of pregnant women to voluntarily participate in a registry are both difficult to predict. Continuous monitoring of patient recruitment rates (comparing projections with observed rates) will allow for strategies to be employed in response to any recruitment challenges.

9.4.4.3 Registry Retention

Registry retention efforts may include general study eNewsletters to HCPs communications that could include: engagement emails, SMS/email/Call reminders, or

'thank you' messages for patients and/or HCPs (where relevant). The projected versus observed drop-out rates will be continuously monitored. Retention planning will be performed in advance as part of the Recruitment Risk Management with triggers for implementation of actions identified, as well as steps to take if the rate of patient completion decreases. Retention efforts for both HCPs and the patients will be documented in the Recruitment and Retention Plan. Steps to ensure recruitment and retention of patients in the Registry include actions for implementation at study start, in addition to actions that could be implemented as the study progresses and new enrollment information becomes available.

9.4.5 Safety Data Collection

All AEs and SAEs in the erenumab-aooe exposed cohort are required to be recorded in the eCRF during the observation period. HCPs will report AEs and SAEs occurring during pregnancy through the infant's first year of life to the CC, who will enter them in the eCRF. See Section 11 for a full description of safety procedures.

9.5 Study Size

The sample size was estimated to assess the prevalence of major congenital malformations in infants of women with migraine exposed to erenumab-aooe during pregnancy and associated risk ratio with the internal comparator. Estimated sample size results ranged from 465 to 4,776 in each treatment group (1:1 exposed vs. unexposed internal comparator) to detect risk ratios ranging from 3 to 1.5, respectively (Table 4). To adequately power an internal comparison of the proportion of major congenital malformation events in the erenumab-aooe exposed, and assuming a 15% drop-out rate and a live birth rate of 62% (FDA, 2002), 1421 erenumab-aooe exposed pregnant women with migraine would need to be enrolled to observe 749 live births. This sample size would provide 80% power to detect a risk ratio of 2.0 or greater in major congenital malformations relative to an assumed prevalence of 3% in the internal comparator cohort (CDC, 2008) at a significance level of α=0.05. Calculations were performed using PASS software version 14.

Given that these numbers assume the prevalence of exposure is sufficient to support recruitment of these numbers, the feasibility of achievement will be re-evaluated at each interim review of the data. The interim analysis planned at year 3 after first patient enrolled and annually thereafter (Section 9.7.1.1), will include sample size re-estimation, examining the observed prevalence and the risk ratio of major congenital malformations

in the erenumab-aooe exposed compared with the internal comparator, accounting for patient recruitment rates and enrollment projections.

Table 4. Sample Size Calculations

Risk Ratio	Estimated Sample Size (with 15% Drop-out and 62% Live Birth Rate)	Estimated Live Births (per Group)
1.5	4776	2517
1.75	2326	1226
2.0	1421	749
2.5	731	385
2.75	573	302
3.0	465	245

9.6 Data Management

IQVIA, the CRO, will be responsible for the data management of this study, this includes designing the eCRFs with input and final approval from Amgen, as well as quality checking of the accuracy, completeness and timeliness of data recorded. The CRO will produce a Data Management Quality Plan and a Data Cleaning Plan that describes the quality checking to be performed on the data. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data. In the event of discrepant data, the CRO will request data clarification from the CC, which the CC will resolve by providing answers to the data queries electronically in the electronic data capture (EDC) system.

Amgen will perform oversight of the data management of this study, including approval of the CRO data management plans and guidance.

The CC will be responsible for data entry into the EDC system. The CC will receive training and have access to a manual for appropriate eCRF completion. All eCRFs should be completed by designated, trained CC staff. eCRFs will be reviewed and electronically signed and dated by the CC Investigator.

eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures. The CRO will comply with Amgen's procedures regarding archiving and record management.

9.6.1 Data Quality Assurance

High data quality standards will be maintained, and processes and procedures will be utilized to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis.

Amgen, CRO representative(s), and regulatory authority inspectors are responsible for contacting and visiting the CC for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data), provided that patient confidentiality is respected. This may also take place remotely by the CRO, as specified in the monitoring plan.

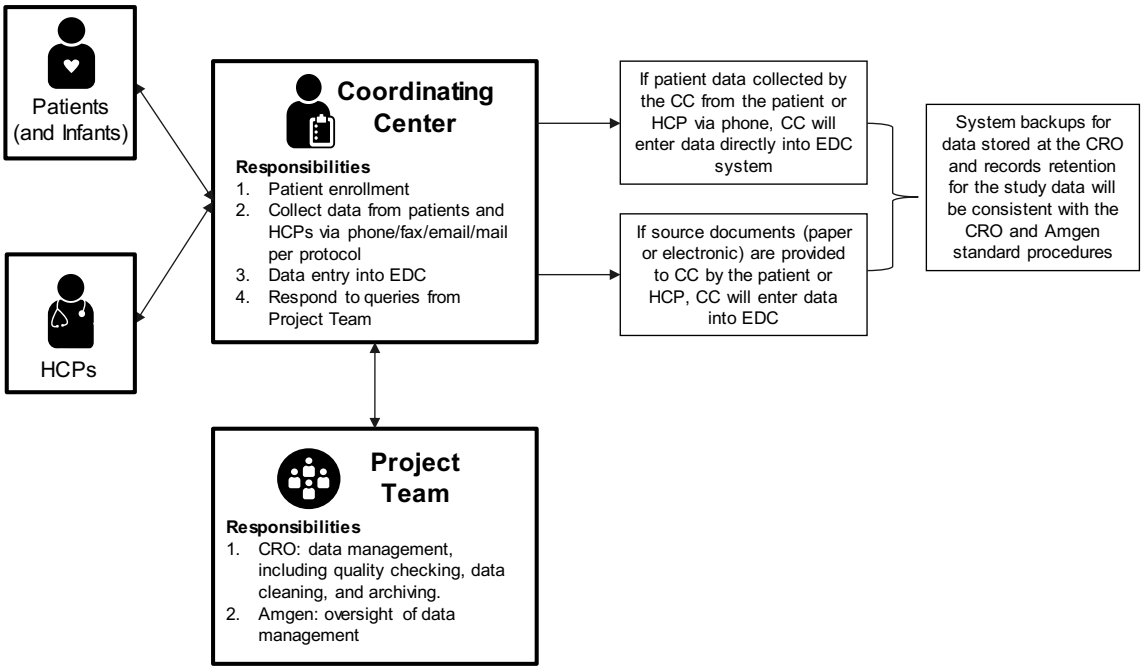
The Clinical Monitor or designee is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol, completeness, accuracy, and consistency of the data, as well as adherence to local regulations on the conduct of research. The Clinical Monitor or designee is to have access to patient medical records and other study-related records needed to verify the entries on the eCRFs 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 eCRFs, are resolved.

In accordance with the Sponsor's audit plans, representatives from Amgen's Quality Compliance and Audit function (or designees) may select this study for audit. Review of study-related records will occur to evaluate the study conduct and compliance with the protocol, and applicable regulatory requirements.

See Figure 1 or data flow overview.

Figure 1. Data Flow Overview



CC = coordinating center; CRO = contract research organization; EDC = electronic data capture; HCP = healthcare provider (eg, PCP, neurologist [indication specialist], OB, nurse midwife, pediatrician); OB = obstetrician; PCP = primary care physician

9.6.2 Review and Verification of Data Quality

Amgen or designee representatives may conduct remote source data verification (SDV) visits as defined in the Study Monitoring Plan at the study facilities for the purpose of monitoring various aspects of the study. Amgen or designee representatives may confirm that critical protocol data (ie, source data) entered in the eCRF by authorized CC personnel into the EDC are accurate, complete, and verifiable from source documents (eg, questionnaires).

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time.

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Study Monitoring Plan. The Study Monitoring Plan defines which kind of source data – if available from clinical routine – can be used for documentation into an eCRF.

Source documents that are required to verify the validity and completeness of data entered in the eCRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 9.8.3.

To facilitate SDV, the CC Investigator must provide direct access to applicable source documents and reports for study-related monitoring, Amgen audits, and Institutional Review Board (IRB) review. The participating CC must also allow inspection by applicable health authorities.

9.7 Data Analysis

9.7.1 Planned Analyses

9.7.1.1 Interim Enrollment Assessment

Regular study updates will be provided in alignment with required safety reporting requirements; anticipated annually. Starting at 3 years following first patient enrolled, an interim analysis will be conducted to assess enrollment and target sample size assumptions, with any needed modifications to patient recruitment and/or retention efforts to be evaluated (see Section 9.4.4). Included as part of the interim analysis, a report will summarize the number of patients enrolled, erenumab-aooe exposure classification information, and describe primary and secondary outcome data.

9.7.1.2 Primary Analysis

The final primary analysis will be conducted once all data collection is complete, including up to 21 months of follow-up for enrolled patients. Annual reports for safety reporting requirements will be generated, with an interim analysis at 3 years.

The primary outcome for this study is the comparison between proportions of major congenital malformations in infants of women with migraine exposed to erenumab-aooe during pregnancy with the unexposed internal comparator. All other outcomes will be classified as secondary. Variables identified for the subgroup analysis will be evaluated as potential confounders in the primary comparative analysis of the risk ratio for major congenital malformations in the erenumab-aooe exposed and unexposed internal comparator.

Data analysis for major congenital malformations will be based on the first trimester exposure to erenumab-aooe. Adjudicated major congenital malformations reported up to 1 year of age by the mother or by an HCP will be included in the primary analysis. Women who have received any first trimester prenatal testing after enrollment, with either negative or positive test result will be included in the primary analysis, ***except***:

- Women who have received first trimester prenatal screening, in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected, because these disorders are unrelated to medication use
- Any prematurity-related disorders and transient conditions
- Women where the outcome is known, prior to enrollment in the registry, either positive or negative, for major congenital malformations that are unrelated to genetic or aneuploid disorders will be analyzed separately as a subgroup analysis.

In addition to the comparison to an unexposed internal comparator cohort, results will be descriptively compared to existing data sources or published reports representing the general population prevalence of birth defects in the general population (see Section 9.2.1.1.1). Additional external data sources for comparison will be considered as they become available during the study.

9.7.1.3 Final Analysis

A final study report will be generated after all data collection is complete, or the study is otherwise terminated, including up to 21 months of follow-up for enrolled patients. The final report will encompass all planned analyses, including a description of the complete study population, as described in Section 9.7.2 and in the SAP.

Details and scope for the final analysis will be described in the SAP.

9.7.2 Planned Method of Analysis

9.7.2.1 General Considerations

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be reported as mean (and standard deviation), median, minimum, maximum and range where appropriate. Categorical variables will be summarized as number and proportion of the total study population, and by subgroups where appropriate. Analyses will be conducted overall (ever exposed during pregnancy) for erenumab-aooe-exposed and internal comparator cohorts as well as by earliest trimester of erenumab-aooe exposure as applicable. If sufficient numbers are obtained, analyses will also be presented by the subgroups of maternal age, race/ethnicity, prior history of elective or therapeutic pregnancy termination status, prenatal screening result (positive versus negative), prenatal testing status (performed vs not performed), exposure to migraine medications of special interest at baseline, and other important risk factors.

Data analysis for major congenital malformations will be based on first trimester exposure to erenumab-aooe. The primary analysis set will exclude women who have received first trimester prenatal screening, in which either aneuploid disorders or genetic disorders that cause major congenital malformations have been detected, because these disorders are unrelated to medication use. Prematurity-related disorders and transient conditions will also be excluded from the analysis of major congenital malformations.

Patient disposition characteristics including descriptive summaries for enrolled patients, patients in the analysis set, completers and early withdrawals with the reasons for early discontinuations will be provided. In addition, demographic information (eg, age, race/ethnicity, BMI), clinical characteristics including comorbidities and medications, other potential factors that may affect pregnancy outcome, and erenumab-aooe exposure will be described.

All computations and generation of tables, listings, and data for figures will be performed using SAS® version 9.2 or higher (SAS Institute, Cary, NC, USA).

9.7.2.2 Missing or Incomplete Data and Lost to Follow-up

Key strategies for minimizing missing or incomplete data and lost to follow-up for pregnancy registries include activities for registry awareness, recruitment and retention (of patients and HCP). Complete details of registry awareness, outreach, and retention efforts will be described in a Recruitment and Retention Plan, and may include the following methods to (1) increase awareness of the registry by using multiple approaches aimed towards HCPs and patients, such as websites, social media, print media, and scientific conferences; (2) evaluate awareness of the registry periodically; (3) accept data from multiple sources; (4) minimize the burden on HCPs; (5) ongoing communications with HCPs and patients; (6) possible compensation for HCPs; and (7) minimize the burden on patients. Compensation will be considered for patients and/or HCPs where allowed by local regulations. All activities in this plan will be reviewed on a regular basis. The strategies for these activities are described in more detail in Section 9.4.4.

It is optimal to prevent missing data, to the extent possible, through strategies set forth in the design and conduct of a study. For the current study, we will aim to minimize missing information by the following:

- Ensuring that primary variables of interest are those that are routinely collected as part of real-world clinical care and are available via medical charts, HCP and/or patient reporting, as appropriate
- Collecting only critical data elements (ie, variables aligned with the study objectives) to minimize patient burden
- Including "not applicable", "not done" on the questionnaires that are being completed by patients/HCPs to differentiate these from values that are truly unknown
- Training of CC staff regarding data collection
- Planning an interim analysis(es) to characterize enrollment and loss to follow-up

- Checking for patterns of missingness and addressing any issues with targeted operational strategies
- Implementing direct to patient strategies to facilitate capture of patient-reported information

Should missing data occur, the data will be analyzed as they are recorded in the study eCRFs. However, the amount of missing values for data elements will be reported and will be assessed for the likely impact of missing data on the analysis and the pattern of the missing information. Full details on handling of missing data will be described in detail in the SAP.

9.7.2.3 Descriptive Analysis

9.7.2.3.1 Description of Study Enrollment

The selection of the study population per analysis set are described in Table 5.

Table 5. Analysis Sets

Analysis Set	Description of Population
Enrolled Set	All women who have signed an informed consent
Full Analysis Set	All women in the Enrolled Set who have any data collected (ie, some study procedures have begun)

9.7.2.3.2 Description of Patient Characteristics

Description of patient characteristics are described in Section 9.7.2.1 (General Considerations).

9.7.2.4 Analysis of the Primary and Secondary Endpoints

The prevalence of major and minor congenital malformations will be calculated using MACDP convention. Major malformations will be analyzed separately from minor malformations, with the primary analysis including only adjudicated major congenital malformations. The total prevalence will be calculated by dividing the number of adjudicated cases of each event (observed in live births, fetal deaths, elective or therapeutic terminations, and at any gestational age) by the total number of pregnancies (excluding spontaneous terminations and ectopic or molar pregnancies). The prevalence at birth will be calculated as number of cases observed in live births and stillbirths divided by the total number of births (stillbirths + live births). Data analysis for major congenital malformations will be based on first trimester exposure to erenumab-aooe.

The prevalence of pregnancy complications, including preeclampsia, pregnancy-induced hypertension, gestational diabetes, placenta previa, and preterm labor, will be summarized by dividing the number of each event by the total number of pregnant women.

The prevalence of spontaneous abortions will be calculated by dividing the number of fetal losses occurring before 20 weeks gestation by the total number of pregnancies.

The prevalence of elective and therapeutic abortion will be estimated similarly as separate outcomes.

Prevalence of preterm birth will be calculated by dividing the number of cases by the total number of births (stillbirths + live births). The prevalence of small-for-gestational-age will be calculated by dividing the number of cases by the total number of live births.

For growth and developmental delays, the prevalence will be calculated as the number of cases divided by the total number of live births.

Prevalence of primary and secondary outcome measures will be presented with 95% CIs for binomial proportion. The analyses summarized in this section will be performed on the erenumab-aooe exposed cohort and the internal comparator cohort consisting of pregnant women with migraine who were not exposed to erenumab-aooe; Characteristics can be matched or stratified in relation to the exposed cohort to control for important covariates such as maternal age (see Section 9.7.2.5.1).

The maternal, fetal, and infant outcomes of women with migraine exposed to erenumab-aooe will be compared with the internal comparator cohort (see Section 9.7.2.5.1). Additionally, the observed prevalence of major congenital malformations will be compared to the external comparator cohort(s) (see Section 9.7.2.5.2).

9.7.2.5 Comparative Analysis

9.7.2.5.1 Internal Comparator Analysis

Primary and secondary outcome frequencies in the erenumab-aooe exposed cohort will be compared with the internal comparator cohort using the risk ratio (95% CIs). Also, comparisons may be explored using ORs adjusted to relevant covariates as applicable, if a sufficient number of outcomes are available in the subgroups. The covariates of interest may include the maternal age, prior history of elective or therapeutic pregnancy termination status, other migraine treatment exposures (such as preventive migraine treatments other than erenumab-aooe), migraine type, and baseline alcohol status. In

addition, erenumab-aooe exposure specific covariates such as any preconception CGRP mAb exposure (> 5 half-lives prior to LMP) and cumulative duration of exposure to migraine therapies during pregnancy may be explored.

Additionally, to assess the impact of exposure on the primary outcomes the propensity score matching may be explored. Baseline characteristics such as age, migraine history (eg, type of migraine), migraine severity (eg, frequency, duration, treatment burden) and parameters of obstetric history will be explored to match between the erenumab-aooe exposed and internal comparator cohorts.

9.7.2.5.2 External Comparator Cohort Analysis

Outcome prevalence for major congenital malformations in the erenumab-aooe exposed cohort will be compared with available external comparator cohort(s) representing the background prevalence of birth defects in the general U.S. population. The MACDP will be the main external comparator cohort (MACDP, 2016; NBDPN, 2010). In the event any European data sources become available for descriptive comparison to this registry, the EUROCAT classification of congenital malformations would be implemented to ensure comparability.

The difference in prevalence of major congenital malformations in erenumab-aooe exposed cohort and the external comparator cohort will be compared similarly as to the internal comparator, with the estimate of risk ratio (95% CIs). Categorical distributions available in the MACDP report will be summarized using the same categories among erenumab-aooe exposed pregnancies (CDC, 2008). Indirect standardization methods will be applied for categorical distributions of maternal age, gestational age, and race/ethnicity. Indirect standardization involves calculation of the observed number of events (ie, major congenital malformations) and applying the maternal age, gestational age, and race ethnicity distributions from the reference population (ie, MACDP) to calculate the expected number of major congenital malformations. The ratio of the observed number of major congenital malformations to the expected number of major congenital malformations is referred to as the standardized prevalence ratio (SPR). Adjusted prevalence can be calculated by multiplying the SPR by the crude congenital malformation rate.

Published EUROCAT reports may be considered as an external comparator; the information would serve as a general non-U.S. population for comparison. Other possible comparisons with external datasets with adjustment methods (ie, direct or indirect adjustment with a standard population) for relevant available categorical

distributions (eg, maternal age, race/ethnicity, gestational age) as noted in Section 9.9.2 will be explored at the time of final analysis. It is important to emphasize that any external comparator data source and women enrolled in this study are two distinctly different, thus "external adjustment methods" for inference comparisons are limited.

9.7.2.6 Sensitivity Analysis

Sensitivity analyses will be performed on both the erenumab-aooe exposed and internal comparator cohorts if sufficient sample size allows, and include but are not limited to the following:

- A sensitivity analysis of major congenital malformations will include women who have received any prenatal screening, regardless of the findings.
- A sensitivity analysis of major congenital malformations will include women where the result is known, regardless of the findings, prior to enrollment in the registry. Subsequently, a sensitivity analysis of major congenital malformations will include women who received any first trimester prenatal screening before enrollment where the result is known to be negative (see Table 2).
- Sensitivity analyses will also be conducted to study the effects of the timing of erenumab-aooe exposure before and during pregnancy and cumulative exposure periods on each outcome.
- A sensitivity analysis of major and minor congenital malformations will be performed that analyzes different cut points of exposure to erenumab-aooe, accounting for each trimester of exposure. While the primary cut point will be the date of LMP to the end of the first trimester (14 weeks gestation), additional sensitivity cut points will include: 16 weeks prior to LMP through the end of the first trimester, LMP date to the end of pregnancy, 16 weeks prior to LMP to the end of pregnancy, second trimester exposure only, and third trimester exposure only.
- Spontaneous abortions defined as occurring before 22 weeks gestation will also be examined in a sensitivity analysis to account for global variation in the definition for this outcome.
- A sensitivity analysis will be performed to examine the impact of time-varying exposure on primary and secondary outcomes. A time-varying exposure cox regression model will adjust for fixed covariates such as maternal age, presence of comorbidities, previous history of obstetric complications, and gestational age at exposure as time varying covariate. Details will be provided in the SAP.
- For spontaneous abortion, a sensitivity analysis will be performed based on gestational age at enrollment.

Sensitivity analyses may rely on sufficient sample sizes in order to execute. Full details will be described in the SAP.

9.7.2.6.1 Subgroup Analysis

Additional subgroups of interest may be explored beyond what is outlined, below. If the difference in subgroups is meaningful, these covariates will be considered for adjustment of confounding in the primary analysis.

- Women in the internal comparator cohort who are migraine treatment naive will be examined separately with respect to the primary and secondary outcomes.
- Both the erenumab-aooe exposed and internal comparator cohorts will be summarized for primary and secondary outcomes both overall and by the subgroups of following parameters, if sufficient sample size allows:
  - Maternal age category
  - Race/ethnicity
  - Smoking status
  - Other classes of migraine therapy used during pregnancy and/or lactation during the infant's first year of life (among live births)
  - Type of migraine: episodic, chronic (with or without aura)
  - Severity of migraine: measured in terms of frequency (occurrence daily, weekly, monthly), time since the date of diagnosis, and presence of aura (ever vs. never), number of prior preventive migraine treatment failures (pre-pregnancy), days of acute migraine treatments each month (pre-pregnancy and by trimester)

9.7.2.6.2 Stratified Analysis

To examine whether other preventive migraine treatment(s) modifies the association between erenumab-aooe exposure and the primary and secondary outcomes, women with documented exposure to another preventive migraine treatment(s) will be examined for significance in a stratified analysis and with an interaction term in the regression model. If an enrolled registry patient is exposed to any potential or known teratogen either before or after enrollment (including any preventive migraine treatments that are known teratogens), or if there is evidence of exposure to any new/emerging teratogen at the time of final analysis, the registry will be analyzed both including and excluding these women at the time of final analysis, with consideration to the timing of exposure during pregnancy and based on the substances' half-lives (ie, during pregnancy or within 5 half-lives prior to the LMP) (Appendix G). Stratification will rely on sufficient sample size, with further details in the SAP.

9.7.2.6.3 Sensitivity Analysis for Residual Confounding and Bias

Not applicable.

9.7.2.6.4 Other Sensitivity Analysis

Not applicable.

9.7.3 Analysis of Safety Outcomes

Interim safety reporting will be conducted every year and will be aligned with the periodic benefit-risk evaluation report (PBRER) reporting schedule. All AE verbatim terms will be recorded and coded using the Medical Dictionary for Regulatory Activities version 21.1 or later. All AEs reported will be analyzed by preferred terms on overall and within erenumab-aooe exposed and internal comparator cohorts.

9.8 Quality Control

9.8.1 Study Documentation

The CC must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited to, the protocol, protocol amendments, ICFs, and documentation of IRB and governmental notification. In addition, at the end of the study, the physician will receive the patient data, which will include an audit trail containing a complete record of all changes to data.

Amgen shall ensure that the dataset and statistical programs used for generating the data included in the final study report are kept in electronic format and are available for auditing and inspection.

9.8.2 Coordinating Center Audits and Inspections

CC inspections may be conducted by Amgen or an authorized representative for audit of study data, patients' medical records, and eCRFs.

The CC Investigator will also permit national and local health authorities to inspect facilities and records relevant to this study.

9.8.3 Retention of Records

At the end of the study, the CC Investigator will receive the data related to patients from his or her CC in an electronically readable format (eg, on a compact disc). Data must be kept with the study records. Acknowledgement of receipt of the data is required.

Retention of study documents will be governed by the contractual agreement with the CRO. At study close, data are uploaded from the database, transferred to Amgen and stored in accordance with Amgen SOPs. Statistical programming and outputs are locked in the analysis environment and no updates are permitted; standard programming procedures will apply.

No records may be disposed of without the written approval of Amgen. Written notification should be provided to Amgen prior to transferring any records to another party or moving them to another location.

All supporting functional parties will comply with Amgen procedures regarding archiving and record management.

9.8.4 External Advisors

A committee of at least 3 qualified, independent teratologists or other appropriate birth defect experts will be used throughout the study for evaluation of congenital malformations and other significant findings. They will be blinded to the patient's exposure status to reduce any potential bias of outcome classification. Other experts in relevant specialties will also be consulted by the Sponsor as deemed necessary by the external advisors.

9.9 Limitations of the Research Methods

Although all possible measures will be taken to ensure the quality and robustness of the data, there are several limitations inherent to the study design that should be acknowledged.

9.9.1 Internal Validity of Study Design

9.9.1.1 Misclassifications

Assessing Exposures: Recall of treatment and other potential exposures that could adversely impact the outcome of pregnancy is subject to variability based on the quality of collection by the HCP or the memory of the patient. Where applicable, calendars will be provided to aid the recall of past exposures. Migraines and migraine treatments (apart from other migraine preventive treatments) are generally episodic in nature. However, because erenumab-aooe is a preventive, injectable therapy, patients are more likely to recall timing of erenumab-aooe exposure as opposed to other migraine treatment interventions due to the indication and mode of administration. Exposure histories could be differential based on exposure.

Assessing the Primary Outcome: A committee of at least 3 qualified, independent teratologists or other appropriate birth defect experts will be used throughout the study for evaluation of congenital malformations and other significant findings in the erenumab-aooe exposed and internal comparator groups to ensure proper classification of the primary outcome (see Section 9.8.4). Adjudicators will be blinded to erenumab-aooe exposure status to ensure if any misclassification remained after adjudication would be non-differential.

Misclassification of the primary and secondary outcomes remain possible, even with independent review. Where applicable, information provided by the HCP will override the information provided by the patient, should there be a discrepancy.

9.9.1.2 Information Bias

Patients who have been informed about a potential adverse pregnancy outcome prior to enrollment in the study may differentially recall their exposures during early pregnancy and may also have changed their exposures after learning of the outcome. This study plans to enroll both women where a fetal diagnosis has been made prior to enrollment in the registry, either positive or negative, for major congenital malformations that are unrelated to genetic or aneuploid disorders), and women with or without prenatal testing prior to enrollment that could determine the status of the fetus) (eg, amniocentesis, genetic testing, nuchal translucency screen, chorionic villus sampling, and late term ultrasound). The differential recall may lead to bias, which will be addressed with the stratification of primary and secondary outcomes by retrospective and prospective status. Additionally, the primary analysis will exclude women who have received first trimester prenatal screening in which either aneuploid disorders or genetic disorders that are known to cause major congenital malformations have been detected.

9.9.1.3 Selection Bias

Spontaneous abortions most frequently occur in early pregnancy, likely before the pregnancy is recognized. Even if the pregnancy is recognized and confirmed, it is possible that the pregnancy may not be reported to the study if the loss occurred before enrollment into the study. Not capturing all early pregnancy losses will likely lead to an underestimation of the true early pregnancy loss rate. There is no reason to believe that this study will be differentially impacted by this bias so even though the spontaneous early losses may be underestimated, the relative rate compared with the other registries should not be affected.

There is potential for channeling bias by label indication due to the severity of migraine at baseline and patient migraine treatment history. Women with more severe migraines may be indicated for erenumab-aooe use compared with women who have less severe migraine histories. Baseline severity of migraine and prior treatments will be captured to assess the degree of confounding by indication.

9.9.1.4 Confounding

Covariates collected in both erenumab-aooe exposed and internal comparator cohorts include the following: pregnancy follow-up and frequency of mother and infant

encounters, medical and medication history (including migraine treatment), migraine history, and pregnancy and infant outcomes (see Appendix F). Careful collection of data elements will be determined based on confounding factors known to be associated with adverse pregnancy outcomes (eg, maternal age, smoking) to examine the distributions between the erenumab-aooe exposed and internal comparator cohorts. The exploration of migraine treatment exposures during pregnancy other than erenumab-aooe, will also be performed by examining specific drugs and/or drug classes. Sensitivity analyses will complement existing primary analysis in controlling for confounding (see Section 9.7.2.5).

9.9.2 External Validity of Study Design

To ensure internal comparability and where feasible, the internal comparator cohort will be recruited from the same clinical centers through HCP awareness and recruitment strategies (see Section 9.2.1) as the erenumab-aooe exposed pregnant women. However, the study population may not be reflective of the broader source population of pregnant women with migraine. Participation in the study is completely voluntary which may select for a particular type of patient group, such as women with severe migraine who have taken medication(s) “at-risk” due to the severity of their condition. Additionally, there are a wide range of treatments for migraine such that the distributions of migraine treatment exposures in the study may not be reflective of the treatment distributions in the source population, which could impact generalizability.

As there are no patient-level data available for the external comparator cohorts, there may be underlying differences between populations that are not detectable. However, reported categorical distributions of maternal age groups, race/ethnicity, or gestational age at birth, may be available for comparison to ensure baseline similarities to the registry population and external adjustment methods (ie, direct or indirect adjustment with a standard population) may be used.

9.9.3 Analysis Limitations

Expected low enrollment may limit the ability to address multiple strata or subgroups due to low sample size. Adequately powered statistical comparisons to the internal comparator cohort of women with migraine who are unexposed to erenumab-aooe could also be impacted by low enrollment; adjustment for covariates may not be feasible. The comparison of the internal comparator cohort to erenumab-aooe-exposed women will be performed and adjusted to relevant covariates, if sufficient number of outcomes are available.

9.9.4 Limitations Due to Missing Data and/or Incomplete Data

Reporting outcomes in this study is voluntary and it is possible that not all patients will complete all of the follow-up assessments. If data from a patient and their HCPs is unattainable, the patient will be considered lost to follow-up. It is possible that the outcomes from pregnancies lost to follow-up could differ from those with documented outcomes. Comparisons of the characteristics of patients with completed information and those lost to follow-up will be conducted in an attempt to address this potential bias.

9.10 Other Aspects

Not applicable.

10. Protection of Human Subjects

The Observational Study will be performed in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practices, Guidelines for Good Pharmacoepidemiology Practices and the applicable legislation on non-interventional studies and/or observational studies. For sites in the U.S., each ICF may also include patient authorization, to allow for the use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA).

The Investigator will perform the Observational Study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the Observational Study and in accordance with currently acceptable techniques and know-how.

10.1 Informed Consent

An initial sample ICF (ICF and ancillary sample ICFs such as Caregiver's ICF, health status data release form [maternal and infant], if applicable) will be provided to each CC to prepare the informed consent document to be used at his or her site. If applicable, it will be provided in a certified translation of the local language. Updates to the template are to be communicated formally in writing from the CRO Clinical Study Manager to the CC.

Before a patient’s participation in the study, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific activities/assessments are conducted. The Investigator or delegated staff must also explain that the patient is completely free to refuse to enter the study or

to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the patient is entitled or is presently receiving.

The acquisition of informed consent and the patient's agreement or refusal of her notification of the PCP is to be documented in the patient's medical records, and the ICF is to be signed and personally dated by the patient and by the person who conducted the informed consent discussion. If a potential patient is illiterate or visually impaired and does not have a legally acceptable representative (LAR), the Investigator must provide an impartial witness to read the ICF to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the ICF to attest that informed consent was freely given and understood.

For the purposes of follow-up with the infant's HCP, the patient will be expected to provide informed consent as a LAR on behalf of the infant. An LAR is an individual or other body authorized under applicable law to consent, on behalf of a patient, to the patient's participation in the study. Where possible, this proxy consent will be included in the patient's informed consent signed at enrollment. Otherwise, prior to the collection and entry of postpartum and through 1-year follow-up data, the physician will be required to obtain informed consent from the patient on behalf of the infant (where required, consent of both parents will be sought). Study staff from the CC will provide reminders to HCPs at appropriate time points to ensure the proxy infant consent is obtained.

By signing the ICF, the patient confirms that she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data, and the possibility of monitoring activities.

A copy of each signed ICF must be provided to the patient. All signed and dated ICFs must remain in each patient's study file or in the site file and must be available for verification by Site Operations Representative at any time.

In the U.S., each ICF may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. HIPAA. If the CC utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply.

10.2 Institutional Review Board

A copy of the protocol, proposed ICFs, other written patient information, and relevant supporting study information must be submitted together to the responsible IRB for its

review. A copy of the written approval of the protocol and all other study documents must be received by the CRO before the study can be initiated. In addition, any patient recruitment materials must be approved by the IRB.

In addition to the requirements for collecting and reporting all AEs and SAEs to Amgen, physicians must comply with requirements for AE reporting to the local health authority and IRB.

The Investigator must submit and, where necessary, obtain approval from the IRB for all subsequent protocol amendments and changes to the informed consent document, as applicable. The Investigator is to notify the IRB of deviations from the protocol in accordance with local procedures.

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

10.3 Patient Confidentiality

The Investigator/CC must ensure that patient confidentiality is maintained for all documents submitted to the CRO. Confidentiality standards will be maintained by coding each patient enrolled in the study through assignment of a unique patient identification number. Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.

Documents that are not for submission to Amgen (eg, signed ICFs, as applicable) are to be kept in confidence by the Investigator, except as described below:

In compliance with local country regulations/International Committee on Harmonisation Good Clinical Practice Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IRB direct access to review the patient's 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 informed consent of the patient to permit such individuals to have access to her study-related records, including personal information.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the ICF (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the U.S. FDA and other national and local health authorities, Amgen monitors, representatives, and collaborators, and the IRB for each CC, as appropriate.

By signing the protocol, the participating physician commits to complying with all related applicable local laws and regulations, including but not limited to the regulations in 45 Code of Federal Regulations parts 160 and 164 (protected health information), such regulations also known as the "HIPAA Privacy Regulations" and the Data Privacy Act.

10.4 Patients Decision to Withdraw

Patients have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Withdrawal of consent for a study means that the patient does not wish to or is unable to continue further study participation. Patient data up to withdrawal of consent will be included in the analysis of the study and, where permitted, publicly available data can be included after withdrawal of consent. The CC is to discuss with the patient appropriate steps for withdrawal of their consent from the study.

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

11.1 Definition of Safety Events

11.1.1 Adverse Events

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

An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a product(s), whether or not considered related to the product(s). The definition of an AE 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 AE is related to an Amgen product prior to reporting the AE to Amgen.

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

11.1.2 Serious Adverse Events

An SAE is any AE as defined above that meets at least 1 of the following serious criteria:

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

Obstetric complications that fall into the above categories are defined as SAEs in this study and should be reported to the CC. Normal delivery and elective cesarean sections performed for non-medical reasons (ie, scheduling, personal preference) and their related hospitalizations will not be considered SAEs, unless, in the view of the reporting physician, the hospitalization was prolonged due to a complication.

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 medically important serious events" refer to important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent 1 of the other outcomes listed in the definition above. Examples of such events could include allergic bronchospasm, convulsions, 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 AE) include the following:

- 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), device(s) or combination products provisioned and/or repackaged/modified by Amgen. Drug(s) or device(s) includes investigational product.

Erenumab-aooe (AIMOVIG®):

- Injection: 70 mg/mL solution in a single-dose prefilled SureClick® autoinjector
- Injection: 140 mg/mL solution in a single-dose prefilled SureClick® autoinjector
- Injection: 70 mg/mL solution in a single-dose prefilled syringe
- Injection: 140 mg/mL solution in a single-dose prefilled syringe

11.2 Safety Collection, Recording and Submission to Amgen Requirements

This study is collecting information from patients and HCPs prospectively from enrollment through the end of follow-up (ie, if the patient is lost to follow-up, consent is withdrawn, death (mother and/or infant), study termination, or the study ends [whichever comes first]). All safety events (AEs, product complaints, and other safety findings) considered to have occurred following patient exposure to erenumab-aooe will be collected from signing of ICF. The CC is responsible for ensuring that all safety events that they become aware of during study period, are recorded in the patient's appropriate study documentation. Those safety events which are considered serious must also be submitted as individual safety reports to Amgen Safety via the applicable Amgen Safety Reporting Form (paper or electronic form) within 1 business day of CC awareness. Non-serious AEs must be reported in an expeditious manner, not to exceed 15 calendars days of CC awareness. Non-serious AEs must be reported in an expeditious manner, not to exceed 15 calendars days of CC awareness. Safety events that are suspected to be related to any medicinal product where there is no exposure to erenumab-aooe should be reported to the local authority in line with the local country requirements.

See Appendix C for sample Safety Report Form(s), Appendix D for Additional Safety Reporting Information regarding the AE grading scale used in this study. The CC 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 in the study documentation where safety data may also be recorded.

11.2.1 Safety Reporting Requirement to Regulatory Bodies

Amgen will report safety data as required in accordance with local requirements to regulatory authorities, Investigators/institutions, IRBs, 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 or other relevant ethical review board of serious AEs in accordance with local procedures and statutes.

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 must be informed of all amendments and give approval. The Investigator **must** send a copy of the approval letter from the IRB 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 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

Amgen will satisfy the requirements for publication of any study results and will submit all study reports to the regulatory health authorities through scheduled PBRERs.

13.1 Publication Policy

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

1. 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, 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.

14. References

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15. Appendices

Appendix A. List of Stand-alone Documents

None

Appendix B. ENCePP Checklist for Study Protocols

European Network of Centres
for Pharmacoepidemiology and
Pharmacovigilance

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title: GENESIS: AIMOVIG® Pregnancy Exposure Registry

EU PAS Register® number: To be determined after final protocol approval

Study reference number (if applicable): 20180125

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

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.1
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.5
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.5
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2.1
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.1, 9.2.2
4.2.2 Age and sex	☒	☐	☐	9.2.4
4.2.3 Country of origin	☒	☐	☐	9.2.1
4.2.4 Disease/indication	☒	☐	☐	9.2.1
4.2.5 Duration of follow-up	☒	☐	☐	9.1, 9.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.4
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.9.1
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9.1
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.9.1

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.2.6.1

Comments:

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

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.2.3
10.4 Are stratified analyses included?	☒	☐	☐	9.7.2.6
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.8.4
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.2
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.2.6

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6.1, 9.8
11.2 Are methods of quality assurance described?	☒	☐	☐	9.6.1, 9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.8.4

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.4.4, 9.7.1.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.2
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.2
13.3 Have data protection requirements been described?	☒	☐	☐	10.3

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

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

Comments:

Name of the main author of the protocol: PPD

Date: dd/Month/year

Signature: _____

Appendix C. Sample Safety Reporting Forms

Observational Research Safety Reporting Form Instructions

This form is for use for observational studies that are using paper report form

General Instructions

The protocol will provide instruction on what types of events to report for the study. *Indicates a mandatory field.

What to report on this form:

- **All adverse events (AEs) are associated with the Amgen drug irrespective of causal relationship of the event to the study drug or seriousness, unless instructed differently by the protocol.**
- **The following safety findings are to be reported on this form as events regardless of association with an AE:**
  - **medication errors, overdose, whether accidental or intentional, misuse, or abuse, involving the Amgen product**
  - **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)**
  - **product complaint (PC)**
  - **adverse device effect (ADE)**

The following should not be reported on this form and should be reported via the normal process set up for the study

- **pregnancy and lactation reports**

1. **Initial or Follow-up*** – Please tick the appropriate box
2. **Site Number*** – Enter your assigned site number for this study. **Subject Number*** – Enter the entire number assigned to the subject.
3. **Indicate event type*** – Tick the relevant box which applies to the event(s) you are reporting. Please note, more than one box can be ticked.
4. **Contact Details*** – Provide your name, phone, address, etc. (These contact details should be for the Vendor or Investigator)
5. **Reporter ID*** – Provide name or ID of reporter, phone, address, etc. (This could be the Investigator details if vendor details are added in section 4.
6. **HCP Contact Details (if other than reporter)*** – Provide name or ID of reporter, country, phone, address, etc.
7. **Patient*** – Enter the subjects demographic information.
8. **Medical History (include primary diagnosis)*** – Enter medical history that is relevant to the reported event, not the event description. This may include pre-existing conditions that contributed to the event, allergies and any relevant prior therapy, such as radiation. Include dates if available.
9. **Suspect Product Information (include dosing details)*** – Provide Product/Device information, Indication, start date, stop date, dose, route, frequency, Lot#, Serial#. It is important that all efforts are taken to provide the Lot number, were possible.
10. **AE, Other Safety Finding, PC/ADE Information*:**

AE Diagnosis or Syndrome*:

- If the diagnosis is known, it should be entered. Do not list all signs/symptoms if they are included in the diagnosis.
- If a diagnosis is not known, the relevant signs/symptoms should be entered.
- If the event is fatal, the cause of death should be entered and autopsy results should be submitted, when available.

Onset Date* – Enter date the AE first started rather than the date of diagnosis or hospitalization. For serious events, the start date is the date the event started, not the date on which the event met serious criteria. **This is a mandatory field.**

Resolved Date* – Enter date the AE ended. For serious events, this is not the date when the event no longer met serious criteria. If the event has not ended at the time of the initial report, a follow-up report should be completed when the end date is known. If the event is fatal, enter the date of death as the end date.

Hospitalization* – If the subject was hospitalized, enter admission and discharge dates. Hospitalization is any in-patient hospital admission for medical reasons, including an overnight stay in a healthcare facility, regardless of duration. A pre-existing condition that did not worsen while on study which involved a hospitalization for an elective treatment, is not considered an AE. Protocol specified hospitalizations are exempt.

Serious Criteria Code* – This is a mandatory field for serious events. Select the appropriate code for the event(s) being reported

Action Taken* – State what action has been taken with suspect drug/device.

Outcome* – Enter the code for the outcome of the event at the time the form is completed if outcome is known.

Severity* – State the severity of the safety event being reported.

Reporter Signature: _____ Page 1 of ____

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Relationship to Product/Device*:

Relationship to Amgen drug under study* – The Investigator must determine and enter the relationship of the event to the Amgen drug under study at the time the event is initially reported.

Relationship to Amgen device* – The Investigator must determine and enter the relationship of the event to the Amgen device (e.g., prefilled syringe, auto-injector) at the time the event is initially reported. **If the study involves an Amgen device, this is a mandatory field. This question does not apply to non-Amgen devices used in the study (e.g., heating pads, infusion pumps)**

11. **Concomitant Medications*** – Indicate if there are any medications.

Medication Name, Start Date, Stop Date, Dose, Route, and Frequency – Enter information for any other medications the subject is taking. Include any study drugs not included in section 5 (Product Administration) such as chemotherapy, which may be considered co-suspect.

Co-suspect – Indicate if the medication is co-suspect in the event.

Continuing – Indicate if the subject is still taking the medication.

Event Treatment – Indicate if the medication was used to treat the event.

12. **Relevant Laboratory Tests*** – Indicate if there are any relevant laboratory values.

For each test type, enter the test name, units, date the test was run and the results.

13. **Other Relevant Tests*** – Indicate if there are any tests, including any diagnostics or procedures.

For each test type, enter the date, name, results, and units (if applicable).

14. **Description*** – Describe Event.

Enter summary of the event. Provide narrative details of the events listed in section 3. Include any therapy administered, such as radiotherapy; (excluding medications, which will be captured in section 6). If necessary, provide additional pages to Amgen.

Complete the signature section at the bottom of each page and fax the form to Amgen.

Reporter Signature: _____ Page 2 of ____

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Project ID: 20180125 *Aimovig (erenumab/AMG 334)*	AMGEN	**Observational Research Safety Reporting Form**	**Date of Reporter Awareness:** **Date Reported to Amgen:**
		Fax reports to: US 1-888-814-8653 or email: svc-ags-in-us@amgen.com	

1. **Initial:** ☐ **Follow-up:** ☐
2. **Site Number:** **Subject Number:**
3. **Indicate event type:** *(Please tick all that apply)* ☐ **AE/Other Safety Finding** ☐ **Product Complaint (PC)** ☐ **Adverse Device Effect (ADE)**

4. Contact Details (Vendor/Investigator)			**5. Reporter ID**		
Name	*Phone*	*Fax*	*Name or ID*	*Phone*	*Fax*
Address			*Address*		
City	*State/Province*		*City*	*State/Province*	
Postal Code	*Country*		*Postal Code*	*Country*	

6. HCP Contact Details (if other than reporter)			**7. Patient**			
Name			*Initials (optional)*	*Sex* ☐ F ☐ M	*Age (at time of event)*	*Was consent obtained to follow-up with HCP?* ☐ Yes ☐ No
Country						
Address						
City	*State/Province*	*Postal Code*	*Weight* ☐ lbs ☐ kg	*Height* ☐ in ☐ cm	*Race*	*Is patient also reporter?* ☐ Yes ☐ No
Phone	*Fax*					

8. Medical History (include primary diagnosis) **9. Suspect Product Information (include dosing details)**

Product/Device: _____

Indication: _____

	Start Date (day month year)	Stop Date (day month year)	Dose	Route	Frequency

Pregnant? ☐ Yes ☐ No Lactating? ☐ Yes ☐ No

Allergy: _____

Prefilled Syringe? ☐ Yes ☐ No

Other Device _____

Lot # _____ ☐ Unknown

Serial # _____ ☐ Unavailable / Unknown

Vial Size

10. AE, Other Safety Finding, or PC/ADE information — **HCP ONLY**

Finding (List main event first; one event per line)	**Onset Date** (day month year)	**Resolved Date** *(If patient died, list date of death)* **Cause of Death:** *(provide autopsy report)* (day month year)	**Hospitalization** Hospitalized? ☐ Yes ☐ No Prolonged Hospitalization? ☐ Yes ☐ No Admitting dx: _____ **Date Admitted** (day month year)	**Date Discharged** (day month year)	**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 significant medical hazard 07 Non-serious	**Action Taken** 1=none 2=dose reduced 3=dose increased 4=drug withdrawn 5=drug rechallenge (state outcome)	**Outcome** 01 Recovered/ Resolved 02 Recovering/ Resolving 03 Not recovered/not resolved 04 Recovered/ resolved with sequelae 05 Fatal 06 Unknown	**Severity** 1=mild 2=moderate 3=severe	**Relationship to Product/Device** Is there a reasonable possibility that this event may have been caused by the Product/Device? Product	Device
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N
									Y N	Y N

Reporter Signature: _____ Page 3 of ____

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11. Concomitant Medications (eg, chemotherapy)

Medication Names	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No	Co-suspect Yes	Continuing No	Continuing Yes	Dose	Route	Frequency	Treatment Meds

12. Relevant Laboratory Values (include dates, allergies, and any relevant prior therapy)

Date Day Month Year	Test / Unit										
	Test										
	Unit										

13. Other Relevant Test (diagnostics and procedures)

Date Day Month Year	Additional Tests	Results	Units

14. Description: Provide chronological summary and details of AE symptoms, PC or ADE that are listed in section 10 (signs, diagnosis, treatment, concomitant medications including those used to treat event).

Reporter Signature: _____ Page 4 of ____

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Appendix D. Additional Safety Reporting Information

Adverse Event Severity Scoring System

For non-oncology studies, the Common Terminology Criteria for Adverse Events (CTCAE) is recommended. The CTCAE is available at the following location: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Appendix E. Data Collection Overview (as per Standard of Care)

Data Collection [a]	Enrollment	Prenatal Follow-Up			Pregnancy Outcome	Pediatric Follow-Up	Early Termination Visit
		End First Trimester (~14 weeks)	Mid Second Trimester (~21 weeks)	Mid Third Trimester (~34 weeks)	~4 weeks after EDD	Infant Age 12, 26, and 52 Weeks	End of Patient Participation in Study
Informed consent [b]	X						
Reporter of information [c]	X	X	X	X	X	X	X
Inclusion/exclusion criteria	X						
Patient demographics and characteristics [d]	X	X	X	X			
Medical history [e]	X						
Pregnancy history, and current pregnancy information [f]	X						
Lifestyle factors [g]	X	X	X	X	X		
Prior and concomitant medications [h]	X	X	X	X	X		
Erenumab-aooe prescription information [i]	X	X	X	X	X		X
Comorbid conditions	X	X	X	X	X		
Migraine and treatment status [j]		X	X	X	X		
Current pregnancy status		X	X	X			X [k]
Gestational age (weeks)	X	X	X	X	X		X [k]
Pregnancy outcome [l]		X	X	X	X		X [k]
Infant characteristics					X [m]	X [n]	X [k]
Infant abnormalities [o]					X	X	X [k]
Patient/infant AEs and SAEs [p]	X ----------→						
Reason for early termination							X

Footnotes defined on next page of table.

AE = adverse event; EDD = estimated date of delivery; HCP = healthcare provider; IRB = Institutional Review Board; LMP = last menstrual period; OB = obstetrician; OTC = over the counter; PCP = primary care physician; SAE = serious adverse event

[a] Available data will be collected; no additional diagnostic or monitoring procedures shall be applied to the patients outside of routine clinical practice.

[b] Written or verbal informed consent must be obtained before any data collection (per local regulations or IRB requirements). If the patient is a minor, written consent must be obtained from the parent or legal guardian.

[c] Including the patient, PCP, OB, neurologist [indication specialist], nurse midwife, infant HCP, other)

[d] Including age of mother, education level, race/ethnicity, height, and pre-pregnancy and current pregnancy weight.

[e] Including surgical and medical history/significant maternal medical conditions other than migraine; migraine history; family reproductive history

[f] Including previous pregnancy outcomes, detailed family history including pregnancy complications, adverse pregnancy outcomes and developmental abnormalities, and information about baseline risks.

[g] Including smoking, use of caffeine, use of alcohol, and use of recreational drugs.

[h] Current and prior medication use starting from 3 months prior to LMP (including all other prescription and any OTC migraine treatment(s), folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities)

[i] Start and stop dates, dose, dosing frequency, reason for discontinuation (if applicable)

[j] Migraine and migraine treatment status since last follow-up

[k] If applicable

[l] Including live births, spontaneous abortions, stillbirths, elective or therapeutic terminations, reason for elective or therapeutic termination (eg, prenatal testing finding, risk to mother's health, undesired pregnancy), mode of birth, and autopsy results and pathology reports, if available

[m] Gestational age, sex, weight, length, head circumference, birth order (for multiple births), Apgar scores, breastfeeding status, vaccination information, infant medications, and any congenital malformation noted, including description and attribution.

[n] Including postnatal growth and development, feeding behavior, weight, length, head circumference, breastfeeding status, vaccine information, and evidence of any abnormality, if applicable.

[o] Detailed information on any infant abnormalities identified after infant birth.

[p] Patient or infant AEs and SAEs (including event, start date, ongoing or end date, seriousness, severity, relationship to erenumab-aooe, outcome, action taken)

Appendix F. Collection of Data Elements

Variables

The tables below further characterize variables corresponding data elements that will be collected during the study, as part of the local routine clinical practice, as available. Variables and variable specifications are subject to change.

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Reporter of Information	Patient	Contact information; Secondary contact (if available)
	PCP	Contact information
	OB	Contact information
	Neurologist (indication specialist)	Contact information
	Nurse midwife	Contact information
	Other (please specify)	Contact information
Eligibility	Informed consent collected from the patient	Date of informed consent also collected
	Age 18 years or older at the time of signing the informed consent form	
	Currently pregnant	
	Is the outcome of the pregnancy (ie, pregnancy loss or live birth) known?	
	Diagnosis of migraine confirmed by the treating physician (ie, neurologist, PCP)	

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Footnotes defined on last page of the table

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Eligibility (Continued)	Erenumab-aooe exposed cohort: Documentation that the patient was exposed to erenumab-aooe starting from 16 weeks or any other CGRP mAb starting from 5 half-lives prior to LMP through pregnancy	
	Internal comparator cohort: Documentation that the patient was not exposed to any CRGP antagonist starting from 5 half-lives prior to LMP or at during pregnancy	Not exposed to erenumab-aooe at any time before or during pregnancy
	Both cohorts: review and confirmation that woman has not taken any topiramate or valproate during pregnancy starting from 1 month prior to LMP	
	Patient agrees to sign the Release of Medical Information Form permitting the study to contact her HCP(s) and the infant HCP for medical information	
	Currently participating in another investigational device or investigational drug study? Currently taking an investigational medicinal product? Has the patient taken an investigational product within 3 months prior to LMP or during pregnancy?	
	Prior to the time of enrollment, has any prenatal testing (eg, amniocentesis, genetic testing, nuchal translucency screen, chorionic villus sampling, and late term ultrasound) been carried out that provides knowledge of the pregnancy outcome?	
	Has the woman enrolled in this registry with a prior pregnancy?	

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Footnotes defined on last page of the table

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Demographics and Characteristics	Maternal age (years)	
	Race	
	Ethnicity	
	Education level	Specify categories
	Height	Units of cm or inches and feet
	Weight (current and pre-pregnancy)	Units of lbs. or kg; current and pre-pregnancy weight, if available
	BMI	Calculated using height and weight
Lifestyle Risk Factors	Cigarette and tobacco use	Current, former, never; if current or former, regular or occasional use?
	Caffeine consumption	Y/N; if yes, how many caffeinated beverages (eg, coffee) per day over the last week?
	Alcohol consumption	Drinks/week
	Illicit drug use	Y/N
Current Pregnancy	Date of LMP	Calendar provided to help recall
	Gestational age at enrollment	
	EDD	Calendar provided to help recall
	Date and results of any prenatal testing	Calendar provided to help recall rubella titer, toxoplasmosis, venereal disease, hepatitis, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein, glucose

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Footnotes defined on last page of the table

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Pregnancy History	Parity	
	Gravidity	
	Previous preterm births	
	Previous spontaneous abortions	
	Previous elective or therapeutic terminations (and reason, if any given)	
	History of any congenital malformations	
	Other (please specify)	Free text field (eg, neonatal sepsis, birth trauma and birth asphyxia)
Surgical History	Past surgical procedures and date(s)	Any
Medical Conditions (other than migraine)	(eg, diabetes, high blood pressure, malignancy)	Includes any current pregnancy complications (eg, preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa)
	Diagnosis	And any test results, if applicable
	Start date(s)	
	End date(s)	
	Disease duration (calculated field)	

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Footnotes defined on last page of the table

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Migraine History	Age at onset of first migraine	
	Diagnosis information	ICHD-III diagnostic criteria
	Type of migraine	Chronic, episodic
	With or without aura	
	If diagnosed with chronic migraine, age at chronic migraine onset	
	Pre-pregnancy: average monthly migraine days, number of prior preventive migraine treatment failures (pre-pregnancy), days of acute migraine treatments each month (pre-pregnancy)	
	Number and duration of migraines and migraine days in the past month (patient-reported)	
	Impact of pregnancy on the intensity of headache	No impact, increased, decreased
Family Reproductive History	Baby's father/Baby's mother's family/Baby father's family -- ever fathered other pregnancies with any of the following;	Y/N
	Multiple births	
	Pregnancy complications	ie, preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa
	Congenital malformations	If yes, please specify
	Spontaneous abortions	
	Premature births	
	Chromosomal anomalies	
	Evidence of developmental delays	

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Footnotes defined on last page of the table

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Erenumab-aooe Treatment	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Prior and Current Medications (all medications used from 3 months prior to LMP)	Name of medication	Multiple entries allowed Including other prescription or OTC migraine treatment(s), folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities
	Indication	
	Start date(s)	
	End date(s)	
	Dose	
Vaccinations Received since LMP	Vaccination (name)	
	Vaccination date (with calendar to aid recall)	

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Footnotes defined on last page of the table

Table 1. Baseline

Variable Category	Data Elements	Additional Information
Patient AEs and SAEs	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to erenumab-aooe	
	Outcome	
	Action taken	

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AE = adverse event; BMI = body mass index; EDD = estimated date of delivery; HCP = healthcare provider; ICHD-III = International Classification of Headache Disorders (3rd Edition); LMP = last menstrual period; mAb = monoclonal antibody; OB = obstetrician; OTC = over the counter; PCP = primary care physician; SAE = serious adverse event

Table 2. Pregnancy Follow-up

Variable Category	Data Elements	Additional Information
Date of Contact		
Reporter of Information [a]	Patient	Contact information (any changes); Secondary contact (if available)
	PCP	Contact information (any changes)
	OB	Contact information (any changes)
	Neurologist (indication specialist)	Contact information (any changes)
	Nurse midwife	Contact information (any changes)
	Other (please specify)	Contact information (any changes)
Lifestyle Risk Factors (if changed since last visit)	Cigarette and tobacco use	Current, former, never; if current or former, regular or occasional use?
	Caffeine consumption	Y/N; if yes, how many caffeinated beverages (eg, coffee) per day over the last week?
	Alcohol consumption	Drinks/week
	Illicit drug use	Y/N
Current Pregnancy	Gestational age at contact	
	Date and results of any prenatal testing	Calendar provided to help recall rubella titer, toxoplasmosis, venereal disease, hepatitis, ultrasounds, amniocentesis, maternal serum alpha-fetoprotein, glucose
	Pregnancy outcome and date of outcome, if applicable	Spontaneous abortion Elective or therapeutic termination (reason for elective or therapeutic termination) Live Birth Stillbirth Congenital malformations identified if spontaneous abortion, termination, or stillbirth; Autopsy and/or pathology reports for adverse pregnancy outcomes of stillbirth, spontaneous abortion or termination will be collected and reviewed, if available.

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Table 2. Pregnancy Follow-up

Variable Category	Data Elements	Additional Information
Medical Conditions (other than migraine since last contact)	Condition	eg, pregnancy complications such as preeclampsia, pregnancy-induced hypertension, preterm labor, gestational diabetes, placenta previa
	Diagnosis	
	Start date(s)	
	End date(s)	
	Disease duration (calculated field)	
Migraine Status (since last follow-up)	Number of migraine episodes since last contact	Date of episodes, number requiring treatment
	With or without aura	
	Days of acute migraine treatments each month	Any prescription migraine treatments
	Frequency and duration of each migraine episode	
Erenumab-aooe Treatment	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	

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Table 2. Pregnancy Follow-up

Variable Category	Data Elements	Additional Information
Other Current Treatments or Concomitant Medications (if applicable)	Medication/treatment name	Multiple entries allowed Including other prescription or OTC migraine treatment(s), folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities
	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
Vaccinations Received since Last Contact	Vaccination	
	Vaccination date (with calendar to aid recall)	
Patient AEs and SAEs	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to erenumab-aooe	
	Outcome	
	Action taken	

AE = adverse event; HCP = healthcare provider; OB = obstetrician; OTC = over the counter; PCP = primary care physician; SAE = serious adverse event
[a] The contact details of the reporter of information will be collected outside of the EDC system at site-level only.

Table 3. Birth Information (approximately 4 weeks after EDD)

Variable Category	Data Elements	Additional Information
Date of Contact	Date	
Reporter of Information [a]	Patient	Contact information (any changes); Secondary contact (if available)
	PCP	Contact information (any changes)
	OB	Contact information (any changes)
	Neurologist (indication specialist)	Contact information (any changes)
	Nurse midwife	Contact information (any changes)
	Infant HCP	Contact information
	Other (please specify)	Contact information (any changes)
Date of Pregnancy Outcome	Date	
	Gestational age (calculated field)	
Pregnancy Outcome	Spontaneous abortion Elective or therapeutic termination (reason for elective or therapeutic termination) Live birth Stillbirth Congenital malformations identified if spontaneous abortion, termination, or stillbirth	Reason for elective or therapeutic termination, if known; Autopsy and/or pathology reports for adverse pregnancy outcomes of stillbirth, spontaneous abortion or termination will be collected and reviewed, if available.
Mode of Delivery	Vaginal delivery Assisted delivery Cesarean section	Anesthesia used, if applicable

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Table 3. Birth Information (approximately 4 weeks after EDD)

Variable Category	Data Elements	Additional Information
Lifestyle Risk Factors (if changed since last visit)	Cigarette and tobacco use	Current, former, never; if current or former, regular or occasional use?
	Caffeine consumption	Y/N; if yes, how many caffeinated beverages (eg, coffee) per day over the last week?
	Alcohol consumption	Drinks/week
	Illicit drug use	Y/N
Medical Conditions (other than migraine since last contact)	Condition	eg, pregnancy complications such as preeclampsia, pregnancy-induced hypertension, preterm labor, Gestational diabetes, placenta previa
	Diagnosis	
	Start date(s)	
	End date(s)	
	Disease duration (calculated field)	
Migraine Status (since last follow-up)	Number of migraine episodes since last contact	Date of episodes, number requiring treatment
	With or without aura	
	Days of acute migraine treatments each month	Any prescription migraine treatments
	Frequency, duration of each migraine episode	
Erenumab-aooe Treatment	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	

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Table 3. Birth Information (approximately 4 weeks after EDD)

Variable Category	Data Elements	Additional Information
Other Current Treatments or Concomitant Medications (if applicable)	Medication name	Multiple entries allowed Including other prescription or OTC migraine treatment(s), folic acid and other vitamins, herbal remedies or supplements, vaccinations, or other medications used to treat chronic conditions or comorbidities
	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
Patient Vaccinations Received since Last Contact	Vaccination and date (with calendar to aid recall)	
Infant Vaccinations Received since Last Contact	Vaccination and date (with calendar to aid recall)	
Infant Characteristics	Date of birth, gestational age at birth (calculated field)	
	Sex	
	Birth weight	
	Length	
	Head circumference	
	Birth order (for multiple births), and number of fetuses	

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Table 3. Birth Information (approximately 4 weeks after EDD)

Variable Category	Data Elements	Additional Information
Infant Characteristics (Continued)	Apgar scores (1, 5, and 10 minutes)	
	Congenital malformations noted (including description and attribution)	
	Infant feeding: breastfed, formula, combination breastfed/formula, other (please describe)	Start and stop dates of exclusive breastfeeding; number of weeks exclusively breastfed since birth (calculated variable)
	Current infant medication(s)	
Patient and Infant AEs and SAEs	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to erenumab-aooe	
	Outcome	
	Action taken	

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AE = adverse event; EDD = estimated date of delivery; HCP = healthcare provider; OB = obstetrician; OTC = over the counter; PCP = primary care physician; SAE = serious adverse event

[a] The contact details of the reporter of information will be collected outside of the EDC system at site-level only.

Table 4. Pediatric Follow-up (approximately at infant age 12, 26, and 52 weeks after birth)

Variable Category	Data Elements	Additional Information
Date of Contact	Date	
Reporter of Information [a]	Patient	Contact information (any changes); Secondary contact (if available)
	PCP	Contact information (any changes)
	Neurologist (indication specialist)	Contact information (any changes)
	Infant HCP	Contact information (any changes)
	Other (please specify)	Contact information (any changes)
Infant Vaccinations Received since Last Contact	Vaccination and date (with calendar to aid recall)	
Infant Characteristics	Length	Value and percentile score
	Head circumference	Value and percentile score
	Weight	Value and percentile score
	Infant feeding: breastfed, formula, combination breastfed/formula, other (please describe)	Number of weeks exclusively breastfed since birth
	Infant developmental milestones: social/emotional, language/communication, cognitive, movement/physical development milestones	Any identified developmental delays or impairment? If yes, please characterize
	Any new malformation or growth alterations since last visit	Including description and attribution

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Table 4. Pediatric Follow-up (approximately at infant age 12, 26, and 52 weeks after birth)

Variable Category	Data Elements	Additional Information
Patient and Infant AEs and SAEs	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to erenumab-aooe	
	Outcome	
	Action taken	

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AE = adverse event; HCP = healthcare provider; OB = obstetrician; PCP = primary care physician; SAE = serious adverse event
[a] The contact details of the reporter of information will be collected outside of the EDC system at site-level only.

Table 5. Early Termination

Variable Category	Data Elements	Additional Information
Date of Contact	Date	
Reporter of Information [a]	Patient	Contact information (any changes); Secondary contact (if available)
	PCP	Contact information (any changes)
	Neurologist (indication specialist)	Contact information (any changes)
	Infant HCP	Contact information (any changes)
	Other (please specify)	Contact information (any changes)
Termination Status	Completion of follow-up Early termination/withdrawal	Date of withdrawal, if different from date of contact. Reason for withdrawal, if provided (lost to follow-up, AE [please specify], or other [please specify])
Reporter of Early Termination	Patient	Contact information (any changes); Secondary contact (if available)
	PCP	Contact information
	OB	Contact information (any changes)
	Neurologist (indication specialist)	Contact information
	Nurse midwife	Contact information
	Infant HCP	Contact information (any changes)
	Other (please specify)	Contact information (any changes)

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Table 5. Early Termination

Variable Category	Data Elements	Additional Information
Date of Pregnancy Outcome	Date	
	Gestational age (calculated field)	
Erenumab-aooe Treatment	Start date(s)	
	End date(s)	
	Dose	
	Dosing frequency	
	Reason for discontinuation (if applicable)	
	Duration of use (calculated field)	
Pregnancy Outcome	Spontaneous abortion Elective or therapeutic termination (reason for elective or therapeutic termination) Live Birth Stillbirth Congenital malformations identified if spontaneous abortion, termination, or stillbirth	Reason for elective or therapeutic termination, if known; Autopsy and/or pathology reports for adverse pregnancy outcomes of stillbirth, spontaneous abortion or termination will be collected and reviewed, if available.

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Table 5. Early Termination

Variable Category	Data Elements	Additional Information
Infant Characteristics	Age	if early termination after birth date
	Sex	
	Birth weight	And current weight, if after birth date; include percentile (if available)
	Length	And current length, if after birth date; include percentile (if available)
	Head circumference	And current head circumference, if after birth date; include percentile (if available)
	Birth defects noted (including description and attribution)	
	Infant feeding: breastfed, formula, combination breastfed/formula, other (please describe)	Number of weeks exclusively breastfed since birth
	Infant development: social/emotional, language/communication, cognitive, movement/physical development milestones	Any identified developmental delays or impairment? If yes, please characterize
	Infant vaccinations received since last contact	Vaccination and date (with calendar to aid recall)
	Current infant medication(s)	
Patient and Infant AEs and SAEs	Event	
	Start date	
	End date	
	Ongoing	
	Seriousness	
	Severity	
	Relationship to erenumab-aooe	
	Outcome	
	Action taken	

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AE = adverse event; HCP = healthcare provider; OB = obstetrician; PCP = primary care physician; SAE = serious adverse event
[a] The contact details of the reporter of information will be collected outside of the EDC system at site-level only.

Appendix G. List of Known Teratogens

This list of known teratogens and their half-lives (last updated as of 15 July 2020) will be used for exclusion purposes in the analysis. This list will be reviewed at the time of analysis to update any changes since protocol finalization.

Substance	Half-Life
Acitretin	49 hours
Azacitidine	41 minutes
Arsenic trioxide	10-14 hours
Ambrisentan	9 hours
Benazepril	10-11 hours
Bosentan	5 hours
Captopril	<3 hours
Carbamazepine	35 hours
Clonazepam	3-40 hours
Cyclophosphamide	3-12 hours
Danazol	9-23.7 hours
Demeclocycline	10-16 hours
Doxycycline	18-22 hours
Dutasteride	5 weeks
Enalapril	14 hours
Enalaprilat	11 hours
Enzalutamide	5.8 days
Ethosuximide	17-56 hours
Finasteride	4.5 hours
Fluconazole	20-50 hours
Fosinopril sodium	12 hours
Fosphenytoin sodium	15 minutes
Indomethacin	4.5 hours
Isotretinoin (systemic)	18 hours
Ledipasvir/sofosbuvir with ribavirin	ribavirin 12 days
Leflunomide	2 weeks
Lenalidomide	13 hours
Lisinopril	12 hours
Lisinopril + hydrochlorothiazide	13 hours

Substance	Half-Life
Lithium	24 hours
Macitentan	14.1-18.5 hours
Methimazole	4.9-5.7 hours
Methotrexate	3-10 hours (lower doses) 8-15 hours (higher doses)
Methylene blue	24 hours
Minocycline	11-24.31 hours
Misoprostol	20-40 minutes
Moexipril	1.3 hours
Paritaprevir/ritonavir/ombitasvir/dasabuvir/ribavirin	ribavirin 12 days
Penicillamine	1-7.5 hours
Phenytoin	12-28.9 hours
Perindopril	30-120 hours
Pomalidomide	9.5 hours
Primidone	7-22 hours
Propylthiouracil	24 hours
Quinapril	25 hours
Quinine	9.7-20 hours
Radium (223Ra) dichloride	11.4 days
Raloxifene	32.5 hours
Ramipril	13-17 hours
Ribavirin	12 days
Riociguat	10 hours
Simeprevir with ribavirin and peginterferon alfa	ribavirin 12 days
Sofosbuvir/velpatasvir with ribavirin	ribavirin 12 days
Sofosbuvir with peginterferon alfa and ribavirin	ribavirin 12 days
Sofosbuvir with ribavirin	ribavirin 12 days
Streptomycin	5-6 hours
Tetracycline	8-10 hours
Teriflunomide	19 days
Thalidomide	5-7 hours
Topiramate	21 hours
Trandolapril	6 hours
Tretinoin (oral)	0.5-2 hours
Trimethoprim	8-10 hours

Substance	Half-Life
Valproate sodium	16 hours
Valproic acid	9-16 hours
Vismodegib	12 days (single dose) 4 days (continuous use)
Warfarin (coumadin)	1 week

Note: This list was generated using the Australian Department of Health Therapeutic Goods Administration (TGA) prescribing medicines in pregnancy database (TGA, 2011; TGA, 2019) and then adapted based on availability in the US market (removing drugs not available in the US and adding teratogens available in the US but not Australia). Lastly, the list was then cross-referenced with Polifka and Friedman (2002) for any FDA-approved prescribing medicines that are designated as known teratogens.