Summary Table of Study Protocol

Title	Observational Study to Assess Maternal, Fetal, and Infant Outcomes Following Exposure to Erenumab-aooe During Pregnancy
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	Aimovig® (erenumab-aooe)
Product Reference	AMG 334
Procedure Number	NA
Joint Post-Authorization Safety Study (PASS)	Yes
Research Question and Objectives	This study is being conducted to understand the safety of administering erenumab-aooe during pregnancy. The primary objective is to estimate and compare the proportion of live-born infants with major congenital malformations among (1) women with migraine directly exposed to erenumab-aooe prior to or during pregnancy, (2) women with migraine exposed to other preventive migraine medications prior to or during pregnancy (comparator group A), and (3) women with migraine not exposed to erenumab-aooe or other preventive migraine medications prior to or during pregnancy (comparator group B). Comparative analyses will be undertaken if there is sufficient sample size and adequate overlap in the distribution of covariates to adjust for confounding. Secondary objectives include estimation and comparison of the proportion of: 1) spontaneous abortions, and, separately, stillbirths, in pregnant women with migraine, and 2) 'small-for-gestational-age,' in live-born infants of women with migraine.
Country(ies) of Study	US
Author	PPD PhD, Amgen, Inc PPD PhD, Amgen Inc PPD PhD, Amgen Inc PPD PhD, HealthCore Inc PPD PhD, HealthCore Inc

Marketing Authorization Holder

Marketing authorization holder(s)	Amgen Inc
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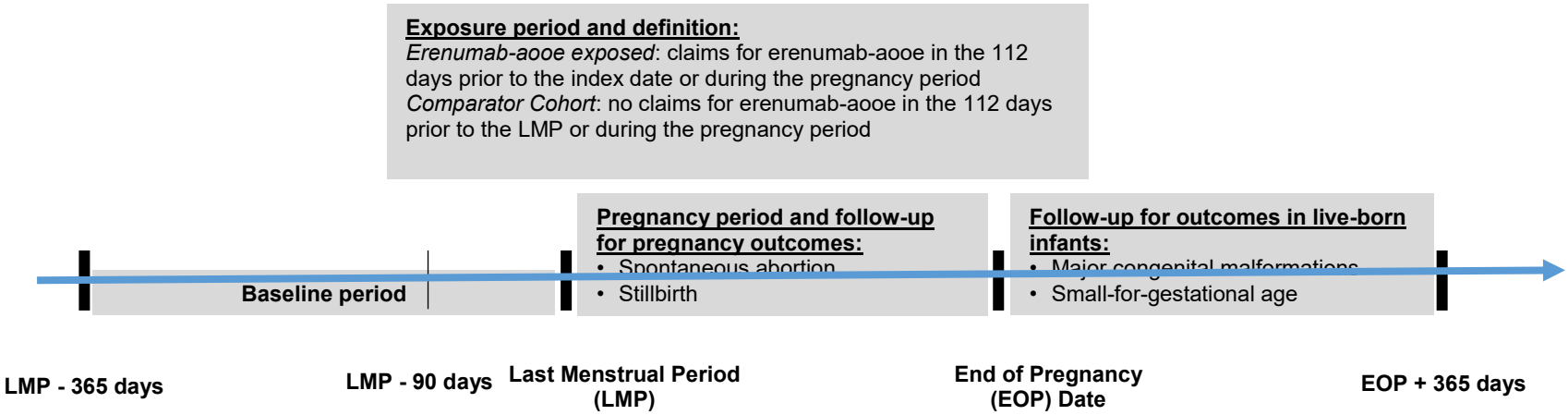
Study Design Schema

Study design: Retrospective observational cohort study using data from MarketScan® Commercial Claims and Encounters databases and the HealthCore Integrated Research Database (HIRD)

Eligibility criteria for pregnant women with migraine: 1) Ages 16-44 years; 2) Evidence (diagnoses or acute medication use) of migraine prior to the last menstrual period (LMP); 3) Complete medical and pharmacy benefits; 4) Continuous health plan enrollment from 365 days prior to the LMP through the end of pregnancy

Eligibility criteria for live-born infants: 1) Infants from eligible pregnant women with migraine with record of live delivery and mother-infant linkage can be established; 2) Continuous enrollment for at least 90 days following birth



Multiple Pregnancies
Women will be followed to capture multiple pregnancies during the study period. Subsequent pregnancy episodes will be identified by applying specific windows of time (min. number of weeks) between eligible pregnancy events outcomes. The length of the time window applied is contingent on type of first and subsequent pregnancy outcome.

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2. List of Abbreviations

ACA	Affordable Care Act
CCE	MarketScan Commercial Claims and Encounters Databases
CFR	Code of Federal Register
CGRP	Calcitonin gene related peptide
CI	Confidence interval
CPT	Common Procedural Terminology
DRG	Diagnostic Related Groups
DSA	Data Sharing Agreement
EDC	Estimated date of conception
EOP	End of pregnancy
EU PAS	European Union Post-Authorization Studies Register
FDA	US Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HIRD	HealthCore Integrated Research Database
HIRE	HealthCore Integrated Research Environment
HIPAA	Health Insurance Portability and Accountability Act
ICD-10-CM	International Classification of Diseases, 10th revision, Clinical Modification
ICMJE	International Committee of Medical Journal Editors
IPTW	Inverse probability of treatment weights
IQR	Interquartile range
LB	Live born
LMP	Last menstrual period
mAb	Monoclonal antibody
MACDP	Metropolitan Atlanta Congenital Defects Program
MRP	Medical record plan
NDC	National Drug Codes
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR	Odds ratio
PASS	Post-authorization safety study
PHI	Protected health information
PPV	Positive predictive value
PS	Propensity score
SAP	Statistical analysis plan
SMD	Standardized mean difference
SD	Standard deviation
US	United States

3. Responsible Parties

PPD PhD, Amgen Inc
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PPD PhD, HealthCore Inc
PPD PhD, HealthCore Inc

4. Abstract

- Study Title: Observational study to assess maternal, fetal, and infant outcomes following exposure to erenumab-aooe during pregnancy
- Study Background and Rationale: Migraine is a neurological disorder characterized by recurrent headache attacks of moderate to severe pain. Erenumab is a human monoclonal antibody (mAb) that inhibits the receptor for calcitonin gene related peptide (CGRP) and is indicated for prevention of migraine headaches. Although clinical trials have demonstrated erenumab has a favorable risk benefit profile, there are no adequate and well-controlled studies on its use in pregnant women with migraine. This study is one of two studies being conducted to address post-market requirements CCI to assess the safety of erenumab-aooe on maternal, fetal, and infant outcomes resulting from the use of erenumab-aooe during pregnancy.

Research Question and Objectives

- Primary Objective
  The primary objective is to estimate and compare the proportion of live-born infants with major congenital malformations among (1) women with migraine directly exposed to erenumab-aooe prior to and during pregnancy, (2) women with migraine exposed to other preventive migraine medications prior to or during pregnancy (comparator group A), and (3) women with migraine not exposed to erenumab-aooe or other preventive migraine medications prior to or during pregnancy (comparator group B). Comparative analyses will be undertaken if there is sufficient sample size and adequate distribution of covariates to adjust for confounding.
- Secondary Objectives
  1) To estimate and compare the proportions of pregnancies ending in spontaneous abortions, and, separately, stillbirths among (1) women with migraine directly exposed to erenumab-aooe prior to and during pregnancy, (2) women with migraine exposed to other preventive migraine medications prior to or during pregnancy (comparator group A), and (3) women with migraine not exposed to erenumab-aooe or other preventive migraine medications prior to or during pregnancy (comparator group B). Comparative analyses will be undertaken if there is sufficient sample size and adequate distribution of covariates to adjust for confounding.

2) To estimate and compare the proportion of live-born infants who are small-for-gestational age among (1) women with migraine directly exposed to erenumab-aooe prior to and during pregnancy, (2) women with migraine exposed to other preventive migraine medications prior to or during pregnancy (comparator group A), and (3) women with migraine not exposed to erenumab-aooe or other preventive migraine medications prior to or during pregnancy (comparator group B). Comparative analyses will be undertaken if there is sufficient sample size and adequate distribution of covariates to adjust for confounding.

3) To describe demographic and clinical characteristics, risk factors for adverse pregnancy outcomes, fetal outcomes, and infant outcomes, and medication treatment patterns during pregnancy in both exposed and unexposed cohorts of women with migraine.

Hypothesis(es)/Estimation

If there is sufficient sample size and adequate overlap in the distribution of confounding variables, we will evaluate the null hypothesis of no effect of treatment on the four outcomes of interest. The proportion of spontaneous abortions, and, separately, stillbirths will be estimated and compared in pregnant women with migraine. Also, the proportion of major congenital malformations and, separately, 'small-for-gestational-age' will be estimated and compared in live-born infants of women with migraine.

Study Design/Type

Retrospective observational cohort study using administrative claims databases.

Study Population or Data Resource

Pregnant women with migraine in the US, ages 16-44 years of age, and who have private insurance. The study will use data from two automated commercial health insurance claims databases. The IBM Watson Health (formerly Truven Health) MarketScan Commercial Claims and Encounters (CCE) Databases includes claims from more than 200 US commercial health plans. The HealthCore Integrated Research Database℠ (HIRD) is a longitudinal claims database with medical coverage for 72.5 million unique individuals, and both medical and pharmacy coverage for 51 million unique individuals.

Summary of Patient Eligibility Criteria

Two cohorts of patients will be followed for outcomes:

1) Pregnant women with migraine, ages 16-44 years at the estimated date of conception
2) Live-born infants of pregnant women with migraine

See Section 9.2.2 for a full list of eligibility criteria.

Follow-up

The study will start in November 2021 and end in November 2028. Because this study uses secondary data that has already been collected, data for analysis will be included starting from May 2018 when erenumab-aooe was approved in the US. Women will be followed for pregnancy outcomes (spontaneous abortion, and, separately, stillbirth) from their estimated LMP date through the end of their pregnancy date, and all live-born infants will be followed for outcomes from birth (eg, small-for-gestational age) through the end of their first year (eg, major congenital malformations). Women with migraine or their infants will be censored when their enrollment in the database ends.

Variables

Outcome Variables
Primary:

Major congenital malformations in live-born infants identified using ICD-10-CM diagnosis codes.

Secondary:

Pregnancies ending in spontaneous abortion, defined as spontaneous losses before 20 weeks of gestation, and identified using ICD-10-CM diagnosis and procedure codes.

Pregnancies ending in stillbirth, defined as *in utero* fetal deaths 20 weeks of gestation and after, and identified using ICD-10-CM diagnosis and procedure codes.

Small-for-gestational age in live-born infants, defined as birth weight 10^{th} percentile, and identified using ICD-10-CM diagnosis codes.

Exposure Variable
Exposure to erenumab-aooe will be defined as having a pharmacy claim for erenumab-aooe (identified through NDC codes) in the 112 days prior to the estimated last menstrual period or during the pregnancy.

Other Covariates
Other covariates will include maternal demographics, reproductive history, comorbidities, concomitant medication use, and other risk factors for adverse maternal, fetal, and infant outcomes.

Validation of select study variables will be performed in the HIRD. Medical record/electronic health records will be sought to validate claims-identified outcomes for major congenital malformations, spontaneous abortion, still birth, and LMP. Similar to other pharmacoepidemiologic database validation studies, this validation study will provide estimates of positive predictive value (PPV) for each of the endpoints. In addition, a validation study of the algorithm to identify migraine cases and estimate the PPV of the algorithm will also be undertaken.

Study Sample Size

In the MarketScan CCE database, feasibility estimates for years 2010-2014 indicate there are annually approximately 7,000 women with migraine who have a pregnancy indicator. In contrast, the HIRD included 11,704 pregnant women with migraine for calendar year 2017. Analyses will be conducted separately for each database and pooled if appropriate. The sample size calculations described below were based on estimates from the Marketscan CCE database, the smaller of the two databases.

We estimate that approximately 0.9% of pregnant women with migraines will be treated with a migraine preventive medication during pregnancy. Based on the projected uptake of erenumab-aooe in migraine patients, we estimate that approximately 1,400-1,500 women with migraine will be exposed to erenumab-aooe during pregnancy in the MarketScan® database for the time period 2018-2027. The actual number will vary depending upon the utilization of erenumab-aooe treatment by the source population in the MarketScan® CCE database. Assuming that we will have an equal number of women with migraine in the comparator cohorts and a background prevalence of the outcome of ≥3%, we will have at least 80% power to detect an odds ratio of 2.00 or higher.

Approximately 75-80% of pregnancies end in live births and taking into account the 77% mother-infant linkage rate in the MarketScan® CCE database, it is estimated that we will have approximately 120 infants for which outcomes may be assessed. As above for pregnancy outcomes, there is limited power to detect moderate differences in outcomes that are relatively rare.

- Data Analysis

  Descriptive interim analyses will be conducted annually, CCI [redacted] The final report will be provided in November 2028. Within each database, for each cohort, these reports will provide overall counts of patients (pregnant mothers and infants), descriptive statistics for baseline patient characteristics, and the proportion (95% confidence intervals [CI]) for outcomes of interest. In addition, occurrence of incident medical conditions (eg, gestational diabetes) and use of new medications during the follow-up period will be summarized.

  Discrete variables will be summarized using frequencies and proportions, and continuous variables will be summarized using means and standard deviations (SD) or medians and interquartile range (IQR), as appropriate.

- Comparative Analyses

  Assuming sufficient power to detect a risk of ratio ≥2.0 and adequate overlap in the distribution of confounding variables, comparative analyses will be initiated. Balance in covariate distributions will be evaluated by standardized mean differences (SMDs), with an SMD < 0.10 indicating good balance. The potential comparative analyses are summarized below:

  (1) Effect of erenumab-aooe versus other preventive migraine medications on spontaneous abortions (and, separately, stillbirths), in pregnant women with migraine.

  (2) Effect of erenumab-aooe versus other preventive migraine medications on congenital malformations (and, separately, 'small-for-gestational-age'), in live-born infants of women with migraine.

  These analyses will be replicated using alternate comparator groups that were unexposed to erenumab-aooe. For the comparative analyses, the effect measure of interest will be the odds ratio (95% CI). We will account for confounding with inverse probability of treatment weights (IPTWs).

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
CCI [redacted]	
Start of data collection	Nov 2020
End of data collection	Nov 2027
Annual interim reports	Nov 2021 – Nov 2027
Registration in the EU PAS register	Oct 2020
Study completion	Nov 2027
Final report of study results	Nov 2028

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; the prevalence peaks in middle life (30 to 49 years) (7.9%-9.0% in men and 25.5%-28.1% in women) and is lower in children/adolescents and those older than age 60 (Lipton et al, 2007).

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, nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, and antiemetic agents (Charles 2017). The most commonly used therapies for migraine prevention include tricyclic antidepressants, beta-blockers, anticonvulsants (eg, topiramate and divalproex sodium), and botulinum toxin (Charles 2017).

Migraine often improves during pregnancy; however, this varies depending on 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).

Up to 70% of pregnant women with migraine require a behavioral or a pharmacologic intervention (Contag et al, 2009). 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 (Robbins 2018). Triptans

are classified as an FDA category C drug. Data from a prospective pregnancy registry observed birth defects in 4.2% (95% confidence interval (CI) 2.6%-6.5%) of infants born to women using sumatriptan during pregnancy (Ephross and Sinclair 2014), which is consistent with general population birth defect rates. Preventive medications that may be used during pregnancy include memantine and beta blockers, such as propranolol (Robbins 2018). Beta-blockers are generally thought to be safe and are commonly used to treat hypertension in pregnant women; however, they may be associated with intrauterine growth restriction (Robbins 2018). Topiramate and valproic acid should be avoided during pregnancy due to their teratogenic effects (Robbins 2018; Hernandez-Diaz et al, 2012).

Erenumab-aooe is a human monoclonal antibody (mAb) that inhibits the receptor for calcitonin gene related peptide (CGRP) and is indicated for the preventive treatment of migraine. Although clinical trials have demonstrated erenumab has a favorable risk benefit profile, there are no adequate and well-controlled studies on the use of erenumab-aooe in pregnant women. In animal reproduction studies, there were no effects on pregnancy or neonatal/infant development when monkeys were administered erenumab-aooe SC from organogenesis through parturition at exposures up to 16-fold the exposure at the maximum recommended human dose of 140 mg monthly.

7.2 Rationale

This study is being conducted to address post-marketing requirements CCI [redacted] to assess the safety of erenumab-aooe on maternal, fetal, and infant outcomes resulting from the use of erenumab-aooe during pregnancy. This proposed study leverages two large US administrative claims databases to allow for longitudinal follow-up of patient outcomes. Additionally, the study will provide an accurate reflection of how patients are treated in community practice settings and assess erenumab-aooe utilization patterns versus other preventive and acute medications being used by pregnant women suffering from migraines.

7.3 Statistical Inference (Estimation or Hypothesis)

If there is sufficient sample size and adequate overlap in the distribution of confounding variables, we will evaluate the null hypothesis of no effect of treatment on the four outcomes of interest. The proportion of spontaneous abortions, and, separately, stillbirths will be estimated and compared in pregnant women with migraine. Also, the proportion of major congenital malformations and, separately, 'small-for-gestational-age' will be estimated and compared in live-born infants of women with migraine.

8. Research Question and Objectives

8.1 Primary

The primary objective is to estimate and compare the proportion of live-born infants with major congenital malformations among (1) women with migraine directly exposed to erenumab-aooe prior to and during pregnancy, (2) women with migraine exposed to other preventive migraine medications prior to or during pregnancy (comparator group A), and (3) women with migraine not exposed to erenumab-aooe or other preventive migraine medications prior to or during pregnancy (comparator group B). Comparative analyses will be undertaken if there is sufficient sample size and adequate distribution of covariates to adjust for confounding.

8.2 Secondary

1) To estimate and compare the proportion of pregnancies ending in spontaneous abortions, and, separately, stillbirths among (1) women with migraine directly exposed to erenumab-aooe prior to and during pregnancy, (2) women with migraine exposed to other preventive migraine medications prior to or during pregnancy (comparator group A), and (3) women with migraine not exposed to erenumab-aooe or other preventive migraine medications prior to or during pregnancy (comparator group B).

Comparative analyses will be undertaken if there is sufficient sample size and adequate distribution of covariates to adjust for confounding.

2) To estimate and compare the proportion of live-born infants who are small-for-gestational age among (1) women with migraine directly exposed to erenumab-aooe prior to and during pregnancy, (2) women with migraine exposed to other preventive migraine medications prior to or during pregnancy (comparator group A), and (3) women with migraine not exposed to erenumab-aooe or other preventive migraine medications prior to or during pregnancy (comparator group B). Comparative analyses will be undertaken if there is sufficient sample size and adequate distribution of covariates to adjust for confounding.

3) To describe demographic and clinical characteristics, risk factors for adverse pregnancy outcomes, fetal outcomes, and infant outcomes, and medication treatment patterns during pregnancy in both exposed and unexposed cohorts of women with migraine.

9. Research Methods

9.1 Study Design

Retrospective observational cohort study

9.2 Setting and Study Population

This study will use data from the following two large commercial claims databases: (1) The Commercial Claims and Encounters (CCE) database from the IBM Watson Health (formerly Truven Health) MarketScan® Research Databases is a large convenience sample of individuals with employer-sponsored private insurance which includes claims from more than 200 US commercial health plans, and (2) the HealthCore Integrated Research Database (HIRD) is a nationwide proprietary, fully integrated, longitudinal commercial clams database with 72.5 million unique individuals. Both claims databases contain information on prescription fills and medical encounters

These databases contain de-identified information on geographically diverse, commercially insured patients in the US. Diagnoses, procedures, and drug dispensings are captured with the following standard coding systems: International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), Common Procedural Terminology (CPT), National Drug Codes (NDC), Healthcare Common Procedure Coding System (HCPCS), and Diagnostic Related Groups (DRGs).

9.2.1 Study Period

The study enrollment period will start in May 2018, when erenumab-aooe was approved in the U.S. and continue through November 2027. Descriptive interim analyses will be conducted annually, CCI [redacted] The final report will be delivered in November 2028. Due to a three to nine-month lag in data availability from administrative claims databases and the planned end of data collection, the final study report will cover the time period from May 2018 through November 2027.

9.2.2 Subject/Patient/Healthcare Professional Eligibility

9.2.2.1 Inclusion Criteria

Two cohorts of patients will be followed for outcomes:

1) Pregnant women with migraine
2) Live-born infants of pregnant women with migraine

Inclusion criteria for the cohort of pregnant women with migraine are as follows:

1) Women who are pregnant and ages 16-44 years of age at estimated LMP date. Pregnancy will be defined using combinations of ICD-10-CM diagnosis codes and CPT procedure codes, which includes having evidence of at least one of the following pregnancy outcomes: spontaneous abortion, stillbirth, live birth, therapeutic abortion, or ectopic pregnancy.
2) Have evidence of migraine during the one year prior to the LMP date or during pregnancy, where migraine is defined using combinations of ICD-10 diagnosis codes for migraine and/or NDC or HCPCS codes for acute migraine medication use (eg, triptans or ergots). Patients will be included if they meet at least one of the following criteria:
    a. 1 migraine diagnosis claim from a "non-emergency" inpatient visit
    b. 1 migraine diagnosis claim from an outpatient visit associated with a neurologist (variable STDPROV 260 in MarketScan CCE)
    c. 1 migraine diagnosis claim from an emergency room visit
    d. 1 outpatient migraine diagnosis claim ***PLUS*** 1 acute migraine drug (triptan or ergot-derivative) prescription claim within 180 days of each other
    e. 2 outpatient migraine diagnosis claims between 7 and 180 days apart
    f. 2 acute migraine drug (triptan or ergot-derivative) prescription claims between 7 and 180 days

    Have complete medical and pharmacy benefits coverage for the twelve months prior to the LMP date through a commercial health plan.

3) Have continuous enrollment in the health plan from 365 days prior to the estimated date of conception through the end of pregnancy

Inclusion criteria for the cohort of live-born infants of pregnant women with migraine are as follows:

1) Live-born infants (based on a live delivery record) from the cohort of pregnant women with migraine. In the HIRD, the subscriber ID is unique for all family members, and infants with birth dates or enrollment records within 30 days of delivery will be matched. Mother-child linkage in the Marketscan CCE database will be determined using the following criteria:
   a. Mother's ID (minus last 2 digits) Infant's ID (minus last 2 digits)
   b. Mother's earliest delivery related claims date (year) from mother's claims records Infant birth year (from infant enrollment records). For mothers with delivery-related claims in December, infants with records in January of the following year will be included.
   c. Infant's first enrollment date is not more than 180 days after mother's delivery related claims
2) Infants must be continuously enrolled for at least 90 days following birth which allows for the assessment of most major congenital birth defects

For comparator cohort A, we will include women who are exposed to other preventive medications during pregnancy as well as before LMP. When considering exposure to other preventive migraine medications before LMP, women will be included if exposure to these substances occurs within five of their half-lives prior to LMP.

9.2.2.2 Exclusion Criteria

Women who are exposed to known teratogens (eg, valproate or topiramate) or other CGRP antagonists will be excluded if exposure to these substances occurs within five of their half-lives prior to LMP.

For comparator cohort B, women who have pharmacy claims for any preventive migraine medications will be excluded.

9.2.3 Matching

For pregnant women with migraine, cohorts will be matched 1:4 on LMP date and gestational age. If there is sufficient sample size and overlap in the distribution of covariates to adjust for confounding, comparative analyses will be conducted, controlling for confounders using inverse probability of treatment weighted analyses.

9.2.4 Baseline Period

The baseline period to assess relevant covariates, such as demographics, comorbidities, and concomitant medications, will be the 365 days prior to the LMP date. To evaluate history of obstetric outcomes (eg, prior pregnancies, multiple gestation, outcomes of prior pregnancies including spontaneous abortions), we will use all available data prior to the index date.

9.2.5 Study Follow-up

The study will start in May 2019 and end in November 2027. Because this study uses secondary data that has already been collected, data for analysis will be included starting from May 2018 when erenumab-aooe was approved in the US. Women will be followed for pregnancy outcomes (spontaneous abortion or stillbirth) from their LMP date through the end of their pregnancy date, and all live-born infants will be followed for outcomes from birth (eg, small-for-gestational age) through the end of their first year (eg, major congenital malformations). Women with migraine or their infants will be censored when their enrollment in the database ends.

9.3 Variables

9.3.1 Exposure Assessment

Pregnant women who have pharmacy claims for erenumab-aooe (identified using NDC codes) in the 112 days prior to the LMP date (to allow for the half-life of erenumab) or during the pregnancy will be considered exposed to erenumab-aooe.

Exposure to erenumab-aooe will be categorized by dose (70 mg versus 140 mg), by length of exposure, and by timing in relation to trimester of pregnancy: before the last menstrual period (LMP, in the 112 days prior to the EDC, this is the exposure window of interest for major malformations), during the first trimester (from the LMP to 90 days after the LMP), during the second trimester (from day 91 after the LMP to day 180 after the LMP), and during the third trimester (from day 181 after the LMP to the end of pregnancy) (see Section 9.3.1.1 for definitions of LMP).

For the comparator cohorts, comparator group A will include pregnant women with migraine who do not have pharmacy claims for erenumab-aooe in the 112 days prior to the LMP but do have evidence of the use of other preventive migraine medications. Comparator group B will include pregnant women with migraine who do not have pharmacy claims for erenumab-aooe or other anti-CGRP medications 112 days prior to the LMP date or during pregnancy

9.3.1.1 Timing of Exposure Assessment

Estimated date of last menstrual period (LMP)

For the calculation of LMP, the following approach will be implemented for all types of pregnancy outcomes, including spontaneous abortion, stillbirth, and live birth.

For the identified end of pregnancy episode, LMP estimation will be based on identifying certain pregnancy-related diagnosis and/or procedure codes and in particular Z3A.®® (Z3A), an ICD-10-CM set of codes that indicate weeks of gestation of pregnancy, with the last 2 characters corresponding to specific weeks of gestation. Even though the Z3A codes are not billable codes, insurance providers, *such as Anthem Blue Cross Blue Shield*, are requiring the reporting of Z3A codes for childbirth delivery claims and especially for early elective procedures (Jamal-Allial et al, 2019). The Z3A code category may serve to more accurately estimate the timing of the pregnancy using administrative claims data. Z3A codes have to be reported alongside the primary pregnancy/delivery code of interest. Because these codes are specific to each week of pregnancy, LMP estimation will be based on the indicated number of weeks of gestation for that reported Z3A code, and an approximate mid-point will be applied, ie, 4 days to each period (Suarez, 2018).

When Z3A codes are not available, weeks of gestation for LMP estimation will be inferred using an algorithm that is informed by algorithms reported in the literature and refined clinical input will be utilized to estimate the corresponding EDC (Hornbrook et al, 2007; Margulis et al, 2013; Margulis et al, 2015; Mines et al, 2014; Ailes et al, 2016). The algorithms reported in the literature assume different lengths of gestation for the different pregnancy outcomes, such as full-term singleton births (40-39 weeks), multiples births (36-40 weeks), stillbirths (20-38 weeks), spontaneous abortions (20 weeks), and ectopic pregnancies (8 weeks). Recognizing these algorithms may over- or underestimate the true gestational age, other codes that indicate weeks of gestation (eg, HCPCS S2260, *induced abortion, 17-24 weeks*) or the trimester of pregnancy (eg, ICD-10 O09.612, *supervision of young primigravida, second trimester*) will be explored. For codes that are associated with a range of gestational age, an approximate mid-point of gestational weeks 4 days will be assigned based on the reported pregnancy-term code, eg, HCPCS S2260: *induced abortion, 17 to 24 weeks*, so the assigned GA is 20.5 weeks 4 days will be used for EDC estimation. Additional details on validation will be provided in the Statistical Analysis Plan (SAP) and the Medical Record Plan (MRP).

End of pregnancy

Pregnancy end will be defined by the date of delivery for live births and non-live outcomes; and by date of admission with an abortive outcome for pregnancies ending in an abortive outcome.

Multiple pregnancies

To adjust for multiple overlapping pregnancy episodes (eg, a spontaneous abortion claim followed by a live birth claim three days later), once a pregnancy outcome is flagged, there will be a standard 15-day period following the pregnancy outcome where no claims will be assessed (eg a subsequent live birth claim will be ignored). See Appendix C for windows to assess pregnancy episodes. Additionally, a fixed window between subsequent pregnancies based on the first and subsequent outcomes will be applied, regardless if it is a live or non-live outcome (Hornbrook et al, 2007). If there are multiple spontaneous abortion or stillbirth events in proximity to one another, the end of pregnancy (EOP) date will be determined using the hierarchy defined below:

1. MarketScan indicators (ED, birthing center, ambulance); not available in HIRD
2. End of Pregnancy (EOP) Procedure Codes (ICD-10-CM & CPT)
3. DRG codes defining EOP
4. Other Procedure codes indicating EOP
5. Other Diagnosis codes defining EOP

In the event of non-live and live pregnancy claims reported on the same date, the non-live outcomes take priority over the live birth claims (unless there is indication of multiple fetuses). If a spontaneous abortion claim occurs on the same date as the stillbirth claim, the stillbirth claim will take precedence. In such cases, a hierarchy is required to select the most relevant claim for any given pregnancy episode.

Subsequent live pregnancy outcomes will be assessed in this manner: apply a specific gap period for preterm and post-term pregnancies (using ICD-10-CM specific diagnosis codes), and a 280-day gap (normal pregnancy duration) preceding any full term live pregnancy outcome to avoid overlapping episodes. The 280-day gap or ICD-10-CM specific gap also applies in the event of the last live pregnancy event occurring during the baseline period. In this case, a gap period is necessary to evaluate the first pregnancy episode. Given that the live pregnancy gap period should be similar to the pregnancy period for the live birth outcome, we would not expect to miss capturing any

non-live birth outcomes during this period. Any non-live birth outcomes occurring during this time period should be noted, but not counted in the analysis.

9.3.2 Outcome Assessment

9.3.2.1 Primary Outcome

Major congenital malformations will be defined overall and by each malformation group using ICD-10-CM codes from the National Birth Defects Prevention Network (NBPDN) birth defects descriptions for the NBPDN core and recommended conditions including:

Central Nervous System (eg, anencephalus, spina bifida without anencephalus, encephalocele)

Eye (eg, anophthalmia/microphthalmia)

Ear (eg, anotia/microtia)

Cardiovascular (eg, common truncus, transposition of great arteries, tetralogy of fallot, ventricular septal defect, atrial septal defect, atrioventricular septal defect, pulmonary valve atresia and stenosis, tricuspid valve atresia and stenosis, Ebstein anomaly, aortic valve stenosis, hypoplastic left heart syndrome)

Orofacial (eg, cleft palate with and without cleft lip, choanal atresia)

Gastrointestinal (eg, esophageal atresia/tracheoesophageal fistula, rectal and large intestinal atresia/stenosis, small intestinal atresia/stenosis)

Genitourinary (eg, renal agenesis/hypoplasia, bladder exstrophy, hypospadias)

Musculoskeletal (eg, clubfoot, limb deficiencies, gastroschisis, omphalocele, diaphragmatic hernia)

See Appendix D for a full list of conditions and ICD-10 diagnosis codes (https://www.nbdpn.org/docs/Appendix_3_1_BirthDefectsDescriptions2015_2016DEC14.pdf). Outcomes that are not associated with drug exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related defects, and positional effects will be excluded from our definition of major congenital malformations. When linked medical records are available for validation studies conducted in the HealthCore Integrated Research Database, we will collect additional information on reasons (ie, chromosomal abnormality) for non-live births, including spontaneous abortions, where available.

9.3.2.2 Secondary outcomes

Spontaneous abortion is defined as loss of the embryo or fetus between conception and the point at which the death would be considered a stillbirth, at week 20 or later (Likis et al, 2013). In the MarketScan CCE database and the HIRD, spontaneous abortion will be identified through ICD-10-CM diagnostic codes and procedure codes (see Appendix E for codes).

Stillbirth is generally defined as intrauterine fetal death on or after the 20th week of gestation, of a fetus weighing 350 grams or more (Likis et al, 2013). Although the date of fetal death may not be known, stillbirth is more likely than spontaneous

abortion to be medically attended, and will be identified through ICD-10-CM diagnostic codes and procedure codes in the MarketScan CCE database and the HIRD (see Appendix F for codes).

Small-for-gestational age in live born (LB) infants, defined as birth weight 10th percentile, will be identified using ICD-10-CM codes in the MarketScan CCE database and the HIRD (see Appendix G for codes).

9.3.3 Covariate Assessment

Study cohorts will be described according to baseline covariates. Demographic attributes will be determined on the cohort entry date while others will be assessed during the baseline period, unless otherwise specified. All covariate information will be ascertained through inpatient and/or outpatient claims for diagnoses and procedures, and through pharmacy claims utilizing ICD-10 CM for diagnoses; ICD-10 PCS, CPT, or HCPCS codes for procedures; and GPI or NDC codes for dispensings. Additional details will be provided in the Statistical Analysis Plan (SAP) and the Medical Record Plan (MRP). Covariates to be assessed include the following:

Maternal age at estimated LMP (in years)

Maternal race, if available

Calendar year at estimated LMP

Geographic region of health plan

Migraine characteristics (eg, migraine with aura, chronic migraine)

Comorbid conditions at baseline (eg, chronic hypertension, hyperlipidemia, diabetes, polycystic ovarian syndrome, hypothyroidism, hyperthyroidism, depression, anxiety, epilepsy), identified through ICD-10-CM diagnosis codes

Medications in the baseline period (eg, acute and preventive migraine treatments, other treatments not for migraine, suspected teratogenic medications), identified through NDC codes or HCPCS codes

Adverse events during pregnancy (eg, pre-eclampsia, gestational diabetes), identified through ICD-10-CM diagnosis codes

Concomitant medications with claims after or a days supply that overlaps the LMP date and by trimester during the pregnancy (eg, acute migraine treatments, other treatments not for migraine, suspected teratogenic medications), identified through NDC codes or HCPCS codes

History of obstetric outcomes (eg, prior pregnancies, multiple gestation, outcomes of prior pregnancies including spontaneous abortions) using all available history

Use of prenatal testing

Resource utilization (eg, number of prenatal visits, types of providers visited, emergency department visits)

Body mass index, if available

Alcohol, tobacco, and substance abuse, if available

Exposure to infections during pregnancy, if available

Previous history of congenital malformations, if available

9.3.4 Validity and Reliability

Identification of pregnancy and timing of exposure assessment during pregnancy

Administrative databases can be useful in the assessment of prenatal drug exposure, and estimation of the LMP is necessary to classify exposure. Incorrect gestational age information can lead to misclassification of medication exposure during specific periods of pregnancy. Since there are no definitive diagnosis codes that clearly indicate the last menstrual period, pregnancy duration, or gestational age, diagnosis and other procedure codes have been recommended and utilized to determine the LMP. Approaches to arrive at the LMP in patients with live birth outcomes has been studied in administrative claims data using ICD-9 coding and have been shown to accurately identify most of these pregnancies (Ailes EC et al, 2016; Margulis AV et al, 2015; Naleway et al, 2013); however, there is no validated approach for pregnancies ending in non-live outcomes, and no studies have examined the impact of changes in ICD-10 coding

We previously tested the feasibility of three approaches (see Appendix B for details) in the MarketScan CCE databases to identify the LMP among pregnancies resulting in fetal death (Hornbook et al, 2007; Kharbanda et al, 2012; Glaxo SmithKline 2017). Results from the feasibility analysis estimating the mean and median gestational age (in weeks) using the three different methods are presented in Table 1. We propose to use an approach like the one described by Hornbrook et al, 2007 which uses outcome-specific estimates of gestational age developed by the Centers for Disease Control and Prevention. The percent agreement between the claims-based algorithm and medical record ranged from 87.5 to 96.3® for non-live birth outcomes (eg, therapeutic abortion, spontaneous abortion, and stillbirth), and from 86.6® to 100® for dates of these non-live birth outcomes.

Table 1. Feasibility Assessment to Estimate Gestational age (in weeks) Based on Three Different Methods

	Method 1 – using gestational age estimates based on national averages from literature (Hornbrook et al, 2007)		Method 2 – using prenatal screening claims prior to pregnancy outcome date (Kharbanda et al, 2012)		Method 3 - triangular distribution to estimate pregnancy episode duration, (Glaxo SmithKline 2017)	
	Estimated gestational age, in weeks					
Pregnancy outcome	**Mean (SD)**	**Median (Range)**	**Mean (SD)**	**Median (Range)**	**Mean (SD)**	**Median (Range)**

Spontaneous Abortion	9.9 (0.7)	10.0 (0.1-10.0)	14.4 (4.5)	13.1 (4.1-30.0)	12.1 (1.2)	12.3 (0.1-13.7)
Stillborn	27.8 (1.7)	28.0 (5.9-28.0)	27.1 (9.4)	26.0 (5.9-48.0)	33.4 (2.4)	33.7 (5.9-35.6)

Mother-infant linkage

Algorithms for linking mothers and their infants in administrative data have been validated in the MarketScan CCE Databases and other claims databases (Hanley and Mintzes, 2014; Kharbanda et al, 2012; Li et al, 2013; Naleway et al, 2013; Palmsten et al, 2013). Linking mother and baby claims is necessary to obtain information on medication exposure during pregnancy, since the infant has no individual pharmacy claims until after birth. Insurance identification numbers typically consist of an encrypted Social Security Number for the primary insured person, plus an additional number for each dependent covered under the primary insured's plan. We will be using the same methods to link mothers and infants as was developed by the FDA Sentinel pregnancy module (Kawai et al, 2017).

Since HealthCore, Inc.-via Anthem, Inc. data-is a major contributor to the Sentinel Collaboration, as of March 2020, HealthCore created a linked Mothers and Infants Table in their HealthCore Integrated Research Environment (HIRE) system which can be used for pregnancy and infants' research. As of March 2019, there are 1.7 million mothers, 3 million infants, and 1.2 linked mothers and infants. HealthCore follows a multi-step process provided by the FDA Sentinel program for creating such tables. The first part is creating Mothers and Infants Table through the Sentinel Modular programs. This is followed by linking the mothers and infants through SubscriberID within DCC and, finally, HealthCore performs quality assurance programing to verify that mothers and infants were correctly linked. The HIRD currently includes around 800,000 mother-infant pairs. In 2017, the HIRD included 11,704 pregnant women with migraine.

Validity of pregnancy and infant outcomes

Although administrative claims data contain diagnosis and procedure codes to identify medically attended maternal and birth outcomes, the positive predictive value (PPV) of these codes varies by outcome, with the majority of PPVs for major congenital malformations ranging from 70-90® (Andrade et al, 2013; Cooper et al, 2008). Algorithms to assess spontaneous abortion and stillbirths have also been developed, and those for stillbirth have shown high PPVs (99-100®) (Likis et al, 2013)

9.3.4.1 Case Validation Plan

Validation will be conducted in the HIRD. Medical record/electronic health records will be sought to validate claims-identified outcomes for major congenital malformations, spontaneous abortion, still birth, and LMP. Similar to other pharmacoepidemiologic database validation studies, this validation study will provide estimates of positive predictive value (PPV) for each of the endpoints. In addition, a validation study of the algorithm to identify migraine cases and estimate the PPV of the algorithm will also be undertaken. Informed by the validation data for the migraine algorithm, sensitivity analyses will be conducted to restrict analyses to patients with an increased probability of having migraine (e.g., increased number and type of migraine diagnosis, treatments and specialist diagnoses) to assess any possible impact on results. The case validation plan will be described in detail in the Medical Record Plan (MRP).

Major congenital malformations will be adjudicated by a birth defects expert/clinical teratologist. Criteria to ascertain each individual malformation will be agreed upon in consultation with the experts, and classification will mirror groupings typically used by the Metropolitan Atlanta Congenital Defects Program (MACDP), noting that MACDP codes are not directly available in the HIRD. The same experts will also support development of abstraction forms for identification of covariate and outcome data and will adjudicate outcomes that are not clearly identifiable from the abstracted data. The two experts will independently review medical records that have been redacted of personally identifying information to determine outcome status. Disagreements will be resolved via discussion or review by a third clinician. Full details of the abstraction, redaction and review processes will be included in the MRP.

The medical records for the spontaneous abortion and still birth will be used to develop detailed case narratives. Medical records would be requested from providers and submitted to clinical experts for adjudication (blinded as to protected health information (PHI) and exposure status).

The medical record retrieval rate is about 60® but varies by study. Outcomes identified in claims where medical records are not available will be classified as provisional outcomes.

9.4 Data Sources

This study will use data from the MarketScan CCE databases and the HIRD. These databases contain fully adjudicated eligibility, pharmacy, procedure, and medical claims data for patients enrolled in large US health plans. The health plans provide coverage

for physician, hospital, and prescription drug services, and capture medical claims or encounter data from all available health care sites (inpatient hospital, outpatient hospital, emergency room, physician's office, surgery center, etc.) for virtually all types of provided services. The coding of medical claims conforms to insurance industry standards, including the use of designated claims forms (eg, physicians use the Health Care Financing Agency [HCFA]-1500 format and hospitals use the UB-92 format). Each record contains information on diagnoses (recorded using the International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM]), procedures (recorded with ICD-10-CM procedure codes, Current Procedural Terminology [CPT] codes, or HCFA Healthcare Common Procedure Coding System [HCPCS] codes). Data are linked at the patient level by a unique identifier that is consistent across services, health plans, and time, and, so, patients can be tracked over multiple years even if they switch health plans. Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. The following pharmacy claims data allow for longitudinal tracking of medication refill patterns and changes in medications used:

National Drug Code (NDC) or HCPCS code
Medication Brand Name
Generic Classification
Medication Strength
Quantity Prescribed
Days of Supply
Fill Date

Undiagnosed conditions, and lifestyle and biometric factors (eg, smoking status) are not well captured in claims data. The data are Health Insurance Portability and Accountability Act (HIPAA) compliant and all data is anonymized.

The MarketScan CCE databases contain data on approximately 17 million employees and their dependents, annually, covered under a variety of fee-for-service and capitated health plans, including exclusive provider organizations, preferred provider organizations (PPOs), point of service plans, indemnity plans, and health maintenance organizations (HMOs).

The HIRD is a large administrative healthcare database maintained by HealthCore for use in health outcomes and pharmacoepidemiologic research. Health care utilization may be tracked for health plan members in the database back to January 2006. As of July 2019, there were 72.5 million unique individuals with medical coverage and more

than 51 million lives with both medical and pharmacy coverage. The HealthCore Integrated Research Environment (HIRE) has the ability to link the claims data in the HIRD to complementary data sources, including inpatient and outpatient medical records from healthcare providers submitting insurance claims, national vital statistics records, cancer and vaccine registries (state-by-state), disease and device registries, individual and provider surveys, point of care clinical data, and clinical oncology data.

9.4.1 Review and Verification of Data Quality

The MarketScan CCE databases are constructed through collection and standardization of raw data from the appropriate payers and linking files across time and data type to create a comprehensive and efficient set of database tables. Variables specific to particular employers are added, as are details on clinical information such as therapeutic class, generic product identifier, therapeutic group, etc. Other enhancements are made to improve the data quality and efficiency, for example: updating diagnosis and procedure codes to reflect changes in codes over time if necessary; creating a common synthetic patient identifier that enables patients to be tracked over time and across data types; integrating benefit plan characteristics, enrollment, outpatient pharmaceutical claims, and medical/surgical data, etc. A comprehensive series of edits on the reasonableness and validity of the data are conducted. For example, checking diagnosis against age and gender, checking charge against payment, checking zip codes, diagnosis and procedure codes against lists of valid values, etc. The verification of data quality follows Marketscan's standard operating procedures (SOPs), which are consistent with the International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices. In particular, the SOPs in place prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication. Data are collected when close to 100® of claims have been paid, which results in a lag time between date of service and date of payment of about six to nine months. No data editing, beyond what is applied in the database production process, will be employed for this study.

The HIRD has implemented the following processes to ensure the accuracy and validity of the data: (1) defining thresholds for completeness and accuracy of key data fields; (2) using per member per month (PMPM) calculations to understand and address emerging data trends (eg, changes in membership types and spend during the introduction of Affordable Care Act [ACA]); and, (3) in addition to the standard QC

checks, such as age and gender checks, the HIRD also undertakes payment and charge checks, address and zip codes checks, diagnosis and procedure codes checks, etc. Due to the HIRD 85® completeness inclusion criteria, the lag time between date of service and date of payment is 3 months. No data editing, beyond what is applied in the database production process described above, will be employed for this study.

The validation for the creation of analytic files from claims data typically involves a combination of a review of SAS program log and output files, independent coding, a review of program processes and documentation to ensure departmental SOPs are followed, and reconciliation of programming code with specifications. Individual programs are documented and revised as needed until sign-off by a validator using a validation/programming log.

9.5 Study Size

Feasibility estimates for the years 2010-2014 indicate that annually we will be able to identify approximately 7,000 pregnant women with migraine from the Marketscan CCE database. In contrast, as of 2017, the HIRD included 11,704 pregnant women with migraine. Analyses will be conducted separately for each database and pooled if appropriate. The sample size calculations described below were based on estimates from the MarketScan CCE database, the smaller of the two databases.

We estimate that approximately 0.9® of pregnant women with migraine will be treated with a migraine preventive medication during pregnancy. Based on the projected uptake of erenumab-aooe in migraine patients, we estimate that from May 2018 through May 2027 approximately 1,400-1,500 pregnant women in the MarketScan CCE database with migraine will be exposed to erenumab-aooe during their pregnancy. The actual number will vary depending upon the utilization of erenumab-aooe treatment by the source population in the MarketScan CCE database.

Sample sizes for the comparison of the primary outcome (major congenital malformations) are calculated assuming a 3® prevalence of major congenital malformations in infants of women with migraine, a 62® live birth rates of pregnancies, 1:4 matching of the erenumab-aooe exposed to the comparator cohorts, and 80® power. In past studies in HIRD involving linkage of mothers and their infants, approximately 72-85® of completed pregnancies could be connected to a qualifying infant (Mines et al, 2014; Nkhoma et al, 2012). In the MarketScan databases, the

mother-infant linkage is approximately 77%. The study will have at least 80% power to detect at least a 2-fold increase in the risk of major congenital malformations (Table 2).

Table 2. Required Sample Size Estimates and Relative Risks for the Comparison of Major Congenital Malformations Between the Erenumab-aooe Exposed Cohort and the Unexposed Cohorts

Relative Risk	Sample size of pregnant women in the exposed group, accounting for 62% live birth rate	Sample size of live births, accounting for a 77% mother-infant linkage rate	Sample size of live births in the exposed group
1.25	11,731	7,273	5,600
1.50	3,142	1,948	1,500
1.75	1,181	909	700
2.00	717	522	425
2.25	597	370	285
2.75	270	208	160
3.00	210	162	125

9.6 Data Analysis

9.6.1 Planned Analyses

9.6.1.1 Primary/Interim Analyses

Descriptive interim analyses will be conducted annually, CCI [redacted]. Within each database, for each cohort, these reports will provide overall counts of patients, descriptive statistics for baseline patient characteristics, and the cumulative incidence proportion (95% CIs) for the outcomes of interest during the follow-up period. In addition, occurrence of incident medical conditions (eg, gestational diabetes) and use of new medications during the follow-up period will be summarized. Beginning with year three, annual reports will also include an assessment of futility for the comparative analyses. Based on sample size calculations for the comparison of the primary outcome of major congenital malformations, at least 425 exposed women who are pregnant will be required to be in this database study to detect a minimum relative risk of 2.00. Futility will be assessed by contextualizing annual counts of women who are pregnant with exposure to erenumab-aooe, and the annual overall count of female patients ages 16-44 years with migraine and exposure to erenumab-aooe. Annual counts of pregnant women exposed to erenumab-aooe will be projected to the end of the study based on historical trends and that year's current use of erenumab-aooe.

9.6.1.2 Final Analysis

The final analysis will be conducted at the end of the study period in November 2028 or when the study is determined to have been completed based on other criteria [redacted]. See Section 9.6.2 for details of the final analysis.

9.6.2 Planned Method of Analysis

9.6.2.1 General Considerations

Each of the primary and secondary outcomes will be described using frequencies, proportions and corresponding 95% confidence intervals (CI). If there is sufficient sample size, formal comparisons to estimate risk (odds ratios (OR) and corresponding 95% CIs) will be undertaken, using inverse probability of treatment weights (IPTWs) to account for confounding Demographic and baseline characteristics, and other covariates will be summarized by cohort of exposure. Discrete variables will be summarized using frequencies and proportions, and continuous variables will be summarized using means and standard deviation (SD) or medians and interquartile range (IQR), as appropriate.

9.6.2.2 Missing or Incomplete Data and Lost to Follow-up

The variables in this study will be measured by searching for diagnosis, procedure, and drug codes. Thus, the data will be captured to the extent that the MarketScan® CCE and the HIRD databases are appropriately populated with these codes. There will be no imputation of missing data. Covariates (eg, maternal race, alcohol use, smoking status) with extensive missing data will be described, but will not be included in regression models. The number of patients (women and infants) who are lost to follow-up when enrollment in the health plan ends will be described.

The use of medical records from HealthCore to confirm and validate the outcomes of interest as well as the timing of the pregnancy is a strength of this study; however, retrieval rates for requested medical records for mothers and/or infants will be less than 100%. We will provide a description of the patients who were excluded due to inability to obtain medical records and their characteristics based on the administrative claims. Additional discussion of the medical records procurement will be described in detail in the MRP.

9.6.2.3 Descriptive Analysis

9.6.2.3.1 Description of Study Enrollment

A summary of the selection of the study population using flow charts with pre-defined inclusion and exclusion criteria will be presented.

9.6.2.3.2 Description of Subject/Patient Characteristics

Demographic and baseline characteristics, and other covariates will be summarized by cohort of exposure. Discrete variables will be summarized using frequencies and proportions, and continuous variables will be summarized using means and standard deviation (SD) or medians and interquartile range (IQR), as appropriate. Prevalent comorbidities will be described at baseline, as well as any incident conditions that occur during the pregnancy (eg, gestational diabetes). Medications used in the year prior to the LMP date, as well as those used during the pregnancy, will be described.

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

9.6.2.4.1 Analysis of the Primary Endpoint

Frequencies and the proportions (95® CIs) of major congenital malformations, in infants born to the following three cohorts of women with migraine, will be estimated: (1) those exposed to erenumab-aooe immediately prior to or during pregnancy, (2) those exposed to other preventive migraine medications immediately prior to or during pregnancy, and (3) those unexposed to any migraine preventive medications, including erenumab-aooe.

If there is sufficient sample size and adequate overlap in the distribution of confounding variables, formal comparisons to estimate odds ratios and corresponding 95® CIs will be undertaken. We will use inverse probability of treatment weights to address confounding. We will fit a logistic regression model for the conditional probability of treatment, $Pr\ (\mathrm{A}_i = a|L_i)$, where L_i is a vector of measured baseline confounders of the exposure and the outcome. The conditional probability of treatment given a set of covariates is commonly referred to as the propensity score (PS), and a histogram of the overlap in the propensity score will be presented. IP of treatment weights will be constructed as:

$$\widehat{W}_i^2 = \frac{1}{\widehat{Pr}(A_i = a|L_i)}$$

For the analyses described here, L_i will be based on subject-matter knowledge (see covariates identified in Section 9.3.3).

9.6.2.4.2 Analysis of the Secondary Endpoints

The proportion of pregnancies ending in spontaneous abortion or stillbirth, and the proportion of live-born infants who are small-for-gestational age in women exposed to erenumab-aooe during pregnancy and in women not exposed to erenumab-aooe before or during pregnancy will be described using frequencies, proportions and corresponding

95® confidence intervals (CI). If there is sufficient sample size and adequate overlap in the distribution of covariates to adjust for key confounders, comparisons will be made using IP-weighted analyses as described in Section 9.6.2.4.1.

9.6.2.5 Sensitivity Analysis

9.6.2.5.1 Subgroup Analysis

Subgroups that will be explored if there is sufficient sample size include maternal age group at LMP (16-17 years, 18-40 years, 41-44 years), calendar year at LMP, comorbidities or medication use at baseline, concomitant medication use during pregnancy, dose of erenumab-aooe taken (70 or 140 mg), and patients who have migraine with aura or chronic migraine.

In addition to assessing outcomes in pregnant women exposed to erenumab-aooe before or during pregnancy and those not exposed to erenumab-aooe before or during pregnancy, we will also explore proportions of each of the outcomes in subgroups of the unexposed cohort, including migraine patients exposed to other CGRPs, migraine patients exposed to erenumab more than 112 days prior to the estimated date of conception and not during the pregnancy, migraine patients exposed to other preventive migraine medications, and migraine patients exposed to known teratogens in the one month prior to or during pregnancy. Also, outcomes will be described in migraine patients with claims for acute medication during the pregnancy.

9.6.2.5.2 Stratified Analysis

None

9.6.2.5.3 Other Sensitivity Analysis

Additional sensitivity analyses are described below:

1. Analyses varying exposure cutpoints and definition of exposure:

For all primary and secondary outcomes, additional subgroups based on timing of exposure will also be assessed, such as women exposed to erenumab during the following time periods: 1) in the 12 or 16 weeks (for the 70mg and 140 mg doses, respectively) prior to or during the pregnancy; 2) at any point during the pregnancy; 3) and in each trimester. The number and timing of erenumab-aooe doses will also be assessed for each outcome.

2. Analyses varying enrollment criteria

Women who have continuous enrollment in the health plan for only 180 days prior to the LMP will also be assessed to allow for more women to be included. Sensitivity analyses relating to missed outcomes arising from non-linkage of the infant data, or infant disenrollment from the health plan will also be conducted. We will evaluate non-linkage at 30 days, at 60 days, and at 90 days to evaluate potential attrition bias as a result of disenrollment. These analyses will be further detailed in the SAP.

3. Quantitative bias analyses

Quantitative bias analyses will be explored to assess the impact of sources of error such as residual confounding, and misclassification of exposures, covariates, or outcomes.

4. Other sensitivity analyses

We will also conduct sensitivity analyses limited to just the first pregnancy, and only among patients with no prior history of adverse pregnancy outcomes.

Patient characteristics and primary and secondary endpoints will also be described in any patients receiving erenumab who do not have a diagnosis for migraine in the chance of off-label use.

Analyses of major congenital malformations will also be conducted in all live born infants (not restricting to those with at least 90 days of follow-up) and limited to infants with at least a year of follow-up/enrollment after birth.

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

This is a study to assess the safety of erenumab-aooe on maternal and fetal outcomes when mothers are exposed to erenumab-aooe during pregnancy. Safety outcomes include major congenital malformations in infants, pregnancies ending in spontaneous abortion or stillbirth, and infants who are small-for-gestational age. The proportion of live-born infants who have major congenital malformations or are small-for gestational age, and the proportion of pregnancies ending in spontaneous abortion or stillbirth will be estimated in an erenumab-aooe-exposed cohort and in an unexposed cohort of pregnant women with migraine.

9.7 Quality Control

For the MarketScan CCE database analyses, the quality assurance process involves review at each step in analytic file build. Reviews of all study programming are performed by a second analytic programmer, including the patient selection and

extraction process, variable definitions, each individual analysis, and table or figure construction.

To help ensure the highest level of quality on every project, HealthCore has established several layers of quality assurance throughout the project lifecycle.

Role Based Control Checks: each member of the team is responsible for performing thorough quality control checks on their work; in addition, the Principal Investigator and Research Project Manager are accountable for quality of all deliverables.

Quality Check Points: centralized “checkpoints” have been implemented during the data management cycle to help ensure accurate translation of programming requests.

Quality Assurance Standards: standard review procedures have been developed and are applied throughout the project lifecycle.

Automation: HealthCore has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability and accuracy for each project.

HealthCore documents study progress, and scientific and quality review of all study activities and deliverables (eg, protocol, data management, data analysis, reports, manuscripts, etc.) in an Action, Decision, Issue, Notification (ADIN) log and in a Quality Control (QC) log. The ADIN log provides documentation of study progress, action items, issues/issue resolution, and notifications, and is updated weekly during internal project team meetings. In addition, the QC Log documents the quality control measures performed for each study activity during the conduct of the study.

All programming required for study database extraction and creation of the analytic datasets from the HIRD will be performed in accordance with HealthCore Programming Standards. The HealthCore Programming Standards are a set of documents describing data extraction methods that are referenced in HealthCore Standard Operating Procedures (SOPs) and provide a guideline for basic, frequently used terms and definitions and respective coding information to maintain operational consistency. Data validation will occur throughout the data management and analysis process. Data quality checks include, but are not limited to, programming checks by an individual who is not the main programmer for the study, internal dataset consistency, and checks to ensure that protocol criteria were met.

9.8 Limitations of the Research Methods

There are several methodological issues associated with the use of administrative claims databases when investigating outcomes of drug exposure during pregnancy. In particular, key challenges relate to the identification of pregnancy episodes, determination of gestational age, the linkage of mothers and infants, and ascertainment of exposures and outcomes; thus, careful interpretation of results is needed in light of study and data limitations.

9.8.1 Internal Validity of Study Design

9.8.1.1 Measurement Error(s)/Misclassification(s)

The algorithm used for identification of pregnancy episodes and outcomes for pregnancies that end in live births is very robust (99® agreement between algorithm and chart review). However, ascertainment of LMP and gestational age for pregnancies ending in spontaneous abortion or stillbirth is challenging. We will use a previously published method, such as Hornbrook et. Al. to estimate gestational age and LMP.

As with any observational study conducted within the context of an insurance claims database, drug exposure and timing of exposure is never entirely certain. Although there is evidence in the claims of patients receiving a prescription dispensing at an outpatient pharmacy, we are unable to verify that patients actually used the medication.

Conversely, pregnant patients may take pills during pregnancy that were obtained from a prescription written and dispensed prior to the conception date. In addition, the prescription database lacks information on non-reimbursable (over-the-counter) analgesics, medication dispensed during hospital admissions, or obtained from the doctor's office as samples.

The completeness and/or sensitivity of some of the covariates of interest, such as body mass index, alcohol, tobacco and substance abuse, and previous history of congenital malformations, may be low, and residual confounding due to these characteristics may still be present.

9.8.1.2 Selection Bias

The generation of mother-infant pairs is dependent on the infant being covered under the same insurer as the mother, and our mother-infant linkage algorithm could only link about 77® of live-born infants to their mothers (based on a completed exploratory analyses). The matched mothers were older (mean age 32.1 years) than the unmatched mothers (mean age 27.2 years), likely because younger mothers are

covered by their parents' health insurance. Other than age, the matched mothers were comparable to the unmatched mothers with regard to geographic region, gestational age, and occurrence of pharmacy dispensation during pregnancy.

The migraine case identification algorithm has not been validated in the MarketScan CCE database. Previously reported literature (Kolodner et al, 2004) and internal validation work in the Pharmetrics and Decision Resources Group claims linked with electronic health record databases showed that the algorithm has very high specificity but low sensitivity. Thus, it is possible that some migraine patients will be misclassified as non-migraine patients and will be excluded from this study. However, use of erenumab-aooe will not likely be missed as migraine diagnosis codes should appear in claims records due to its insurance coverage requirements.

Women will be followed through their pregnancy, and their live-born infants will be followed for one year after birth, or until the end of enrollment in the database. It is possible that we may miss outcomes if enrollment ends prior to the outcome. Differential loss to follow-up is a type of selection bias that poses a potential threat to the internal validity of any study. Loss to follow-up can be broadly conceptualized as any termination of treatment prior to the administrative end of the study, including, but not limited to, drop-out as a result of change in health plan, drop-out due to illness/frailty. For our study, we consider only health plan disenrollment. If all disenrollment occurred at random there would be loss in precision, but no increase in bias of the effect estimate. In most studies using claims data, we assume that health plan disenrollment does not occur at random. We will use sensitivity analysis to evaluate the potential impact of attrition bias.

9.8.1.3 Confounding

Confounding by baseline covariates will be addressed with the use of inverse probability of treatment weights. We rely of subject matter knowledge to include candidate confounding variables in our analyses, but residual confounding may exist as a result of unmeasured or incomplete confounders (eg, obesity, use of alcohol, smoking, illicit drug use) or unknown confounders. We will include even weak confounders in the final analysis, sacrificing precision of our final effect estimates by guarding against the potential bias that might be introduced by omission of the confounder. The approach to address unmeasured confounders is addressed in section 9.8.4.

9.8.2 External Validity of Study Design

This study is limited to individuals with employer-sponsored health coverage included in the MarketScan CCE and the HIRD databases. Thus, results of this analysis may not be generalizable to individuals with other type of insurance coverage or those without health insurance.

9.8.3 Analysis Limitations

As described in Section 9.8.1.3, there is the potential for unmeasured confounding due to variables that cannot be measured in the administrative claims database.

9.8.4 Limitations Due to Missing Data and/or Incomplete Data

Women will be followed through their pregnancy, and their live-born infants will be followed up through one year after birth, or until the end of enrollment in the database. It is possible that we may miss outcomes if enrollment ends prior to the outcome.

9.9 Other Aspects

Beginning with year three, annual analyses will include an assessment of futility.

10. Protection of Human Subjects

The data used in this study will not involve the interaction with or interview of any subjects, and the data does not include any individually identifiable data. All database records are de-identified and fully compliant with the United States patient confidentiality requirements, including the HIPAA act of 1996.

HealthCore will maintain Data Sharing Agreements (DSAs) and Business Associate Agreements with covered entities that provide Protected Health Information (PHI) incorporated into the HIRD. HealthCore's access, use, and disclosure of PHI are in compliance with the Health Insurance Portability and Accountability Act (HIPAA), Privacy Rule [45 Code of Federal Register (CFR) Part 160 and Subparts A and E of Part 164]. HealthCore does not access, use, or disclose PHI other than as permitted by HIPAA and its Business Associate Agreements. When using PHI for research, this typically means PHI will be used to create limited data sets for research, or when that is not feasible we may obtain a specific waiver of the HIPAA authorization requirements from an institutional review board (IRB). HealthCore also takes into consideration other federal and state laws and regulations that might limit use of certain types of data more than HIPAA, including those laws related to identifiable records related to substance abuse and human immunodeficiency virus (HIV).

The current study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the US, with health information to be obtained from medical records. Protected Health Information (PHI) must be accessed from medical records in order to adjudicate the outcomes of interest. A HIPAA Waiver of Authorization will be applied for from an IRB prior to any PHI identification. PHI will be redacted from medical records prior to any adjudication activities (further described in medical record plan).

At no time during the conduct of this study will HealthCore provide individual or provider identifying information to the Sponsor. Only de-identified aggregated results will be reported to Amgen Inc. Amgen will not attempt to re-identify any results provided for the study. There will be no active enrollment or active follow-up of study subjects for this study.

All parties should comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at HealthCore's Wilmington, DE office in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. HealthCore will implement appropriate technical and organizational measures to ensure that the person data can be recovered in the event of interest.

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

This study is analyzing secondary data from the IBM Watson Health (formerly Truven Health) MarketScan Research Databases and from the HealthCore Integrated Research Database (HIRD), which are administrative claims databases. The safety outcomes that are listed in Section 9.3.2 will be documented in the administrative claims and analyzed in this study. These will be reported in aggregate in the final study report as proportions and odds ratios. See Section 9.3.2 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

Amgen may amend or terminate the protocol with agreement from the FDA.

13. Plans for Disseminating and Communicating Study Results

13.1 Publication Policy

The results of the 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 (ICJME) 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, and 3 and 4.

   When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.

   Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.

   All persons designated as authors should qualify for authorship, and all those who qualify should be listed.

   Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review.

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15. Appendices

Appendix A. ENCePP Checklist for Study |

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

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 as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Observational study to assess maternal, fetal, and infant outcomes following exposure to erenumab-aooe during pregnancy

Study reference number: 20170172

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 Study progress report(s)	☐	☐	☒	
1.1.4 Interim progress report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS register	☒	☐	☐	6

[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 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
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:	☒	☐	☐	7.2
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.2
2.1.2 The objective(s) of the study?	☒	☐	☐	8
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	8

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (eg, cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3 Does the protocol specify measures of occurrence? (eg, incidence rate, absolute risk)	☒	☐	☐	9.6.2.4
3.4 Does the protocol specify measure(s) of association? (eg, relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.6.2.4
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	9.2.1
4.2.2 Age and sex?	☒	☐	☐	9.2.2
4.2.3 Country of origin?	☒	☐	☐	9.2
4.2.4 Disease/indication?	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up?	☒	☐	☐	9.2.5
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	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? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.4
5.3 Is exposure classified according to time windows? (eg, current user, former user, non-use)	☒	☐	☐	9.3.1
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.1

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? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	9.3.4

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.8.1.3
7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.8.1.3
7.2 Does the protocol address:	☐	☐	☐	
7.2.1. Selection biases (eg, healthy user bias)	☒	☐	☐	9.8.1.29. 8.1. 2
7.2.2. Information biases (eg, misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.8.1.1
7.3 Does the protocol address the validity of the study covariates?	☒	☐	☐	9.3.4

Comments:

Section 8: Effect modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.6.2.5

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? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
9.1.3 Covariates?	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.1
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
9.3.3 Covariates?	☒	☐	☐	9.3.3
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.6.2
10.2 Are descriptive analyses included?	☒	☐	☐	9.2.3
10.3 Are stratified analyses included?	☐	☒	☐	
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.6.2.4
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.6.2.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☐	☒	☐	
11.2 Are methods of quality assurance described?	☒	☐	☐	9.7

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.8
12.1.2 Information bias?	☒	☐	☐	9.8
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.8
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	9.5

Comments:

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

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?	☒	☐	☐	12

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	13

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
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

Signatur: _____

Appendix B. Feasibility Assessment and Comparison of Methods for Timing of Exposure Assessment During Pregnancy

Administrative databases can be useful in the assessment of prenatal drug exposure, and estimation of the LMP date is necessary to classify exposure. Incorrect gestational age information can lead to misclassification of medication exposure during specific periods of pregnancy. Since there are no definitive diagnosis codes that clearly indicate the last menstrual period, pregnancy duration, or gestational age, diagnosis and other procedure codes have been recommended and utilized to determine the last menstrual period (LMP). Approaches to arrive at the LMP in patients with live birth outcomes have been thoroughly studied in administrative claims data and have been shown to accurately identify most of these pregnancies (Ailes EC et al, 2016; Margulis AV et al, 2015; Naleway et al, 2013); however, there is no validated approach for pregnancies ending in non-live outcomes.

We previously tested the feasibility of three approaches in the MarketScan CCE databases to identify the LMP among pregnancies resulting in fetal death (Hornbook et al, 2007; Kharbanda et al, 2012; Glaxo SmithKline 2017). To test the first approach (Hornbrook et al, 2007), we assigned outcome-specific gestational age estimates based on national averages from the literature (Martin et al, 2003; Copper et al, 1994). Assigning a fixed estimate (eg, patients with stillbirths were assigned a gestational period of 28 weeks) yielded no variability in the gestational age assignment among patients with identical outcomes, which did not accurately reflect the true date of the LMP. However, the approach provided solutions to address pregnancy durations that were incompatible with the respective pregnancy outcomes, overlapping pregnancy episodes, and subsequent pregnancy episodes, which are described in more detail in Section 9.3.1.1).

An alternative approach (Kharbanda et al, 2012) flagged prenatal screening claims prior to the pregnancy outcome date to arrive at the LMP. This method was developed under the assumption that the prenatal screenings were expected to occur at specified time points during the pregnancy episodes (eg, nuchal screenings are generally 12 weeks from the LMP). Significantly fewer prenatal screenings were recorded during pregnancy episodes terminating in non-live outcomes than live births, particularly among those ending in spontaneous abortion. This is likely due to shorter pregnancy episodes characteristic for mothers with non-live outcomes. Additionally, the frequency of screenings was dependent on the outcome, and the relative timing between screenings

(eg, from nuchal screen to triple screen) in the MarketScan database was inconsistent with the assumptions specified by the authors.

Lastly, we implemented a triangular distribution (described in a protocol from Glaxo SmithKline, Glaxo SmithKline 2017) which included predefined distribution parameters (minimum, median, and maximum) specific to the outcome in efforts to estimate the pregnancy episode duration.

Appendix C. Minimum Number of Weeks Required to Identify Separate Pregnancy Episodes

	→First Outcome										
Second Outcome ↓	LB	SB	LB & SB	Ectopic	Tropho-blastic dx	Spontaneous abortion	Induced abortion	Abortion, type unknown	LB or SB	Early loss, outcome unknown	LB, SB, or Abortion
LB	24	24	24	22	22	20	20	20	24	20	20
SB	24	24	24	22	22	20	20	20	24	20	20
LB & SB	24	24	24	22	22	20	20	20	24	20	20
Ectopic	10	10	10	8*	8	6	6	6	10	6	6
Tropho-blastic dx	10	10	10	8	Review	6	6	6	10	Review*	6
Spont. abortion	10	10	10	8	8	6	6	6	10	6	6
Induced abortion	10	10	10	8	8	6	6	6	10	6	6
Abortion, type unknown	10	10	10	8	8	6	6	6	10	6	6
LB or SB	24	24	24	22	22	20	20	20	24	20	20
Early loss, outcome type unknown	10	10	10	8*	Review	6	6	6	10	Review*	6
LB, SB, or Abortion	10	10	10	8	8	6	6	6	10	6	6

* Review if 12 weeks

Source: Hornbrook et al, 2007, supplemental information. https://onlinelibrary.wiley.com/doi/abs/10.1111/j.1475-6773.2006.00635.x

Appendix D. ICD-10-CM and CPT Procedure Codes to Identify Outcomes: Major Congenital Malformations*

ICD-10-CM diagnosis or CPT procedure codes	Description of codes
	Central Nervous System
Q00.0-Q00.1	Anencephalus
Q05.0-Q05.9, Q07.01, Q07.03 w/o Q00.0 - Q00.1	Spina bifida without anencephalus
Q01.0 – Q01.9	Encephalocele
	Eye
Q11.0 – Q11.2	Anophthalmia / microphthalmia
	Ear
Q16.0, Q17.2	Anotia/microtia
	Cardiovascular
Q23.0	Aortic valve stenosis
Q21.1	Atrial septal defect
Q21.2	Atrioventricular septal defect (Endocardial cushion defect)
Q25.1	Coarctation of the aorta
Q20.0	Common truncus (truncus arteriosus or TA)
Q20.1	Double outlet right ventricle (DORV)
Q22.5	Ebstein anomaly
Q23.4	Hypoplastic left heart syndrome
Q25.2, Q25.4	Interrupted aortic arch (IAA)
Q22.0, Q22.1	Pulmonary valve atresia and stenosis
Q20.4	Single Ventricle
Q21.3	Tetralogy of Fallot (TOF)
Q26.2	Total anomalous pulmonary venous connection (TAPVC)
Q20.3, Q20.5	Transposition of the great arteries (TGA)
Q22.4	Tricuspid valve atresia and stenosis
Q21.0	Ventricular septal defect
	Orofacial
Q30.0	Choanal atresia
Q37.0 – Q37.9	Cleft lip with cleft palate
Q36.0 – Q36.9	Cleft lip alone (without cleft palate)
Q35.1 – Q35.9	Cleft palate alone (without cleft lip)
	Gastrointestinal
Q39.0 – Q39.4	Esophageal atresia/tracheoesophageal fistula
Q42.0 – Q42.9	Rectal and large intestinal atresia/stenosis
Q41.0 – Q41.9	Small intestinal atresia/stenosis

* Using the core and recommended birth defects from the NBDPN list of birth defects descriptions (https://www.nbdpn.org/docs/Appendix_3_1_BirthDefectsDescriptions2015_2016DEC14.pdf)

ICD-10-CM diagnosis or CPT procedure codes	Description of codes
	Genitourinary
Q64.10, Q64.19	Bladder exstrophy
Q64.12	Cloacal exstrophy
Q64.2	Congenital Posterior Urethral Valves
Q54.0 – Q54.9 (excluding Q54.4)	Hypospadias
Q60.0 – Q60.6	Renal agenesis/hypoplasia
	Musculoskeletal
Q66.0, Q66.89	Clubfoot
Q79.0, Q79.1	Diaphragmatic hernia
Q79.3	Gastroschisis
Q71.0 – Q71.9, Q72.0 – Q72.9, Q73.0 – Q73.8	Limb deficiencies (reduction defects)
Q79.2	Omphalocele

* Using the core and recommended birth defects from the NBDPN list of birth defects descriptions (https://www.nbdpn.org/docs/Appendix_3_1_BirthDefectsDescriptions2015_2016DEC14.pdf)

Appendix E. ICD-10-CM and CPT Procedure Codes to Identify Outcomes: Spontaneous Abortion

ICD-10-CM diagnosis or CPT procedure codes	Description of codes
O03	Spontaneous abortion
O03.0	Genital tract and pelvic infection following incomplete spontaneous abortion
O03.1	Delayed or excessive hemorrhage following incomplete spontaneous abortion
O03.2	Embolism following incomplete spontaneous abortion
O03.3	Other and unspecified complications following incomplete spontaneous abortion
O03.30	Unspecified complication following incomplete spontaneous abortion
O03.31	Shock following incomplete spontaneous abortion
O03.32	Renal failure following incomplete spontaneous abortion
O03.33	Metabolic disorder following incomplete spontaneous abortion
O03.34	Damage to pelvic organs following incomplete spontaneous abortion
O03.35	Other venous complications following incomplete spontaneous abortion
O03.36	Cardiac arrest following incomplete spontaneous abortion
O03.37	Sepsis following incomplete spontaneous abortion
O03.38	Urinary tract infection following incomplete spontaneous abortion
O03.39	Incomplete spontaneous abortion with other complications
O03.4	Incomplete spontaneous abortion without complication
O03.5	Genital tract and pelvic infection following complete or unspecified spontaneous abortion
O03.6	Delayed or excessive hemorrhage following complete or unspecified spontaneous abortion
O03.7	Embolism following complete or unspecified spontaneous abortion
O03.8	Other and unspecified complications following complete or unspecified spontaneous abortion
O03.80	Unspecified complication following complete or unspecified spontaneous abortion
O03.81	Shock following complete or unspecified spontaneous abortion
O03.82	Renal failure following complete or unspecified spontaneous abortion
O03.83	Metabolic disorder following complete or unspecified spontaneous abortion
O03.84	Damage to pelvic organs following complete or unspecified spontaneous abortion
O03.85	Other venous complications following complete or unspecified spontaneous abortion
O03.86	Cardiac arrest following complete or unspecified spontaneous abortion
O03.87	Sepsis following complete or unspecified spontaneous abortion
O03.88	Urinary tract infection following complete or unspecified spontaneous abortion
O03.89	Complete or unspecified spontaneous abortion with other complications
O03.9	Complete or unspecified spontaneous abortion without complication
O02.1	Missed abortion
59820	Treatment of missed abortion, completed surgically; first trimester
59812	Treatment of incomplete abortion, any trimester, completed surgically
59821	Treatment of missed abortion, completed surgically; second trimester
59830	Treatment of septic abortion, completed surgically

Appendix F. ICD-10-CM and CPT Procedure Codes to Identify Outcomes: Stillbirth

ICD-10-CM diagnosis or CPT procedure codes	Description of codes
O36.4	Maternal care for intrauterine death
Z37.1	Single stillbirth
Z37.3	Twins, one live born and one stillborn
Z37.4	Twins, both stillborn
Z37.6	Other multiple births, some live born
Z37.7	Other multiple births, all stillborn

Appendix G. ICD-10-CM and CPT Procedure Codes to Identify Outcomes: Small-for-gestational age

ICD-10-CM diagnosis or CPT procedure codes	Description of codes
P05.1x	Newborn small for gestational age
P05.x	Newborn light for gestational age
P07.0x	Extremely low birth weight newborn
P07.1x	Other low birth weight newborn