# PASS Information

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| Title: | Observational Cohort Study of Exposure to Galcanezumab during Pregnancy |
| Study identifier: | I5Q-MC-B003 |
| Version identifier: | Version 1.0) |
| Date of last version: | NA |
| EU PAS Register No: | EUPAS27574 |
| Active substance: | Galcanezumab; ATC code: N02CX08 |
| Medicinal product(s): | Galcanezumab 120-mg solution for injection |
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| Procedure number: | EMEA/H/C/004648 |
| Marketing authorisation holder(s): | Eli Lilly and Company |
| Joint PASS: | No |
| Research question and objectives: | The primary objectives of this study are to:<br>• Monitor and describe exposure to galcanezumab during pregnancy in women with migraine or cluster headache,<br>• Monitor and describe exposure to other medications indicated for migraine prophylaxis during pregnancy in women with migraine,<br>• Describe the incidence of pregnancy, maternal and infant outcomes among pregnant women exposed to galcanezumab for migraine and cluster headache or other medications for migraine prophylaxis in routine clinical practice in the United States (US).<br><br>The pregnancy, maternal and fetal/infant outcomes of interest include:<br>(1) Pregnancy outcomes: recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery.<br>(2) Maternal outcomes: hypertension during pregnancy, and pre-eclampsia.<br>(3) Fetal/infant outcomes: small for gestational age, major and minor congenital malformations. |

Approval Date: 22-Nov-2019 GMT

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| | The secondary objective if a sufficient number of women with migraine who are exposed to galcanezumab during pregnancy and their linked infants are identified, is to conduct comparative safety analyses of pregnancy, maternal and fetal/infant outcomes between pregnant women with migraine exposed to galcanezumab to the following comparator groups:<br>(1) Women with migraine exposed to any of a composite of other migraine prophylactic medications (amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, and nadolol) during pregnancy (primary analysis).<br><br>(2) Women diagnosed with migraine who were not exposed to any migraine prophylaxis medications during pregnancy (secondary analysis):<br>a. Pregnant women with migraine treated with triptans.<br>b. Pregnant women with migraine and prior history of calcitonin gene-related peptide (CGRP)-inhibitor use, who discontinued therapy at least four months prior to the start of pregnancy<br>(3) A population of commercially insured pregnant women without migraine diagnosis and without exposure to galcanezumab. |
| Country(-ies) of study: | United States |
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# Marketing Authorisation Holder

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| Marketing authorisation holder (MAH) | Eli Lilly Nederland B.V.,<br>Papendorpseweg 83,<br>3528BJ Utrecht,<br>The Netherlands |
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## List of Annexes

# 2. List of Abbreviations

| Abbreviation | Term |
|---|---|
| **AE** | Adverse event |
| **AR** | Adverse reaction |
| **ATC** | Anatomical therapeutic chemical |
| **BMI** | Body mass index |
| **CGRP** | Calcitonin Gene-Related Peptide |
| **CI** | Confidence interval |
| **CPT** | Current Procedural Terminology |
| **CV** | Cardiovascular |
| **DALY** | Disability-adjusted life year |
| **EMA** | European Medicines Agency |
| **ENCePP** | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| **ERB** | Ethical review board |
| **EU** | European Union |
| **FDA** | Food and Drug Administration |
| **GPI** | Generic Product Identifier |
| **HCPCS** | Healthcare Common Procedure Coding System |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **HIRD** | HealthCore Integrated Research Database |
| **HIRE** | HealthCore Integrated Research Environment |
| **HRQoL** | Health-related quality of life |
| **ICD-9-CM** | International Classification of Diseases, Ninth Revision, Clinical Modification |
| **ICD-10** | International Classification of Diseases, Tenth Revision |
| **IHS** | International Headache Society |
| **IR** | Incidence rate |
| **IRB** | Institutional Review Board |
| **IRR** | Incidence rate ratio |
| **LMP** | Last menstrual period |

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|---|---|
| **MACDP** | Metropolitan Atlanta Congenital Defects Program |
| **MAH** | Marketing authorisation holder |
| **MCM** | Major congenital malformation |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MI** | Myocardial infarction |
| **NSAIDs** | Non-steroidal anti-inflammatory drugs |
| **PAS** | Post-authorisation studies |
| **PBRER** | Periodic benefit-risk evaluation report |
| **PPV** | Positive predictive value |
| **PSUR** | Periodic safety update reports |
| **QALY** | Quality adjusted life years |
| **SAP** | Statistical Analysis Plan |
| **TIA** | Transient ischemic attack |
| **US** | United States |

# 3. Responsible Parties

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# 4. Abstract

**Title**
Observational Cohort Study of Exposure to Galcanezumab during Pregnancy among Women with Migraine

Version 1.0
PPD

**Rationale and background**
Galcanezumab is a humanized monoclonal antibody that binds to calcitonin gene-related peptide (CGRP) and prevents its biological activity without blocking the CGRP receptor. Galcanezumab is approved by the United States (US) Food and Drug Administration (FDA) and the European Commission for the prophylactic treatment of migraine in adults. Galcanezumab is administered once monthly as a subcutaneous injection. It is anticipated that, given the treated patient population and the long half-life of galcanezumab (27 days), exposure during pregnancy may occur in the post authorization setting.

**Research question and objectives**
The primary objectives of this study are to:

- Monitor and describe exposure to galcanezumab during pregnancy in women with migraine or cluster headache.
- Monitor and describe exposure to other medications indicated for migraine prophylaxis during pregnancy in women with migraine.
- Describe the incidence of pregnancy, maternal and infant outcomes among pregnant women exposed to galcanezumab for migraine and cluster headache, or other medications for migraine in routine clinical practice in the US.

The pregnancy, maternal and fetal/infant outcomes of interest include:

(1) Pregnancy outcomes: recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery;
(2) Maternal outcomes: hypertension during pregnancy, and pre-eclampsia; and
(3) Fetal/infant outcomes: small for gestational age, major and minor congenital malformations.

The secondary objective is, if a sufficient number of women exposed to galcanezumab during pregnancy and sufficient number of infants linked to the exposed to pregnancies are identified, is to conduct comparative safety analyses for pregnancy, maternal and fetal/infant outcomes comparing pregnant women with migraine exposed to galcanezumab to various comparator groups of women with migraine unexposed to prophylactic migraine medication and women with migraine receiving other prophylactic migraine medications.

**Study design**

This is a cohort study using secondary data from administrative commercial insurance claims and will include two phases:

- Phase 1: We will monitor, describe patient characteristics, and provide counts of study outcomes among pregnant women with migraine or cluster headache exposed to galcanezumab or other migraine prophylactic medications.

  Uptake monitoring will occur annually from 2020-2026. After each monitoring cycle, overall patient accrual will be compared against the target sample sizes estimated to detect at least a two-fold difference in the risks of pre-eclampsia and major congenital malformations with at least 80% power to determine feasibility for Phase 2.

- Phase 2: If the target sample size is reached, we will conduct comparative analyses for pregnancy, maternal and infant outcomes, comparing galcanezumab-exposed pregnancies with comparator pregnancies. Exposure, outcome, and covariate data will be identified primarily using administrative claims, while certain lifestyle covariates will be ascertained via medical record review. If the target sample size is not reached, only descriptive statistics and outcome rates will be calculated for the exposed and comparator groups.

**Population**

Phase 1: For descriptive analyses, we will identify a cohort of women exposed to galcanezumab during pregnancy, defined as receiving at least one dispensing during or within four months before the start of pregnancy. Exposure to other migraine prophylactic medications will be defined as receiving at least one dispensing during pregnancy or the pre-pregnancy period. The relevant pre-pregnancy period for the comparator medication cohort will be determined with a data driven approach and will depend on the medication utilization patterns within the claims database. Medication dispensings will be identified through pharmacy or medical claims in the HealthCore Integrated Research Database (HIRD) and having continuous health plan enrolment for at least 180 days prior to the estimated start of pregnancy. The galcanezumab cohort will be stratified into cluster headache and migraine cohorts based on whether the patient had a diagnosis of cluster headache or migraine prior to the beginning of her pregnancy.

Phase 2: The choice of comparator for this study is particularly challenging given the known associations of some prophylactic migraine medications with congenital malformations and other study outcomes. In order to overcome the limitations of any single comparator group, several have been considered. Primary analyses will focus on an active comparator group. We will conduct comparative analyses if patient accrual reaches the target size for the galcanezumab exposed cohort. Regardless of whether this target size is reached, we will identify and describe the following comparator groups:

(1) Women with migraine with exposure to other migraine prophylaxis medications during pregnancy (primary analyses):

Pregnant women with at least one diagnosis of migraine and who are treated with at least one other medication used for migraine prophylaxis (amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, or nadolol) prior to pregnancy and until the end of pregnancy, noting that medications known to be associated with a given outcome will be excluded from analysis of that outcome (e.g., valproate will be included in analysis of pre-eclampsia but excluded from analyses of major congential malformations). The exposure window prior to pregnancy will be determined by calculating the median days between claims to empirically ascertain how dispensing patterns within the HIRD will affect the length of the washout period.

(2) Women diagnosed with migraine who were not exposed to any migraine prophylaxis medications during pregnancy (secondary analyses):

a. Pregnant women with at least one diagnosis of migraine and at least one dispensing of a triptan in during pregnancy or the pre-pregnancy window (to be determined in a similar manner as the prophylactic migraine medication cohort).

b. Pregnant women with at least one diagnosis of migraine and a prior history of CGRP-inhibitor use, who were not dispensed CGRP-inhibitors during or within four months prior to the start of pregnancy.

(3) A population of commercially insured pregnant women without migraine diagnosis and without exposure to galcanezumab.

**Variables**

In Phase 1, exposure to galcanezumab and other migraine prophylaxis medications will be ascertained from claims for outpatient pharmacy dispensings, as well as codes for injections that are administered in a health care setting. Outcomes and covariates, including demographics, clinical characteristics, healthcare utilization, and concomitant medication use, will be ascertained using administrative claims from the HIRD.

In Phase 2, if comparative analysis is initiated, exposures, outcomes and covariates, including demographics, clinical characteristics, healthcare utilization, and medication use will additionally be ascertained using medical record data. We will obtain medical record data to confirm study outcomes and the timing of the start of a random sample of pregnancies. Covariates not widely available in the administrative claims, such as lifestyle factors (e.g., smoking status, body mass index, alcohol use) will also be sought from medical records for all individuals in the galcanezumab and active comparator cohorts.

**Data sources**
This study will be conducted using the HIRD, which includes longitudinal medical and pharmacy claims data from members of a commercial health insurance plan across the US. All available data prior to the start of the pregnancy will be used to assess baseline characteristics. Claims will be utilized as the data source for exposure status, endpoints and covariates, if available. Medical records will be utilized to confirm outcomes and covariates that are incompletely captured in claims, such as body mass index (BMI) and smoking and alcohol use.

**Study size**
Infant/Fetal Outcomes:
The available number of exposed pregnancies will depend on the uptake of galcanezumab among pregnant women in the HIRD. Assuming that major congenital malformations occur in approximately 3% of births in the general population [4], a 4:1 ratio of comparator: galcanezumab, and a z-alpha of 1.96, we would have 80% power to detect a relative risk of 2.00 with 430 galcanezumab-treated mother-infant pairs and approximately 1,800 unexposed pairs.

Maternal Outcomes:
Assuming that pre-eclampsia occurs in approximately 3% of pregnancies in the general population [5], a 4:1 ratio of comparator: galcanezumab, and a z-alpha of 1.96, we would have 80% power to detect a relative risk of 2.00 with 430 galcanezumab-treated pregnant women and approximately 1,800 unexposed pregnant women.

**Data analysis**
In Phase 1, the number of women of child-bearing age, pregnant women, and mother-infant pairs who are exposed to galcanezumab for migraine and cluster headache and other migraine prophylaxis medications will be identified. Patients in the galcanezumab cohort will further be categorized into cohorts and sub-cohorts defined by diagnosis/treatment of migraine or cluster headache. We will monitor uptake and describe distributions of covariates including demographics, comorbidity, medications, and health care utilization overall, and separately stratified by cohort/sub-cohort defined by diagnosis/treatment of migraine or cluster headache. The incidence rates or birth prevalences, along with the 95% confidence intervals (CIs) of the pregnancy, maternal and fetal/infant outcomes will be presented. These rates and prevalences will also be stratified by cohort/sub-cohort defined by diagnosis/treatment of migraine or cluster headache among the galcanezumab exposed cohort.

In Phase 2, if feasible, we will conduct a propensity score matched analysis to compare the incidence of maternal and fetal/infant outcomes between patients with migraine exposed to galcanezumab during pregnancy to each of the four comparator cohorts.

Probability of exposure based propensity scores will be used to balance baseline covariates to facilitate comparisons between the galcanezumab cohort and the four comparator groups. Distinct propensity scores will be estimated for each comparator group. Propensity scores will be generated using logistic regression and will include baseline covariates captured in the claims

data, as well as from medical record abstraction, when available. We will use standardized differences to check the balance of potential confounding variables between exposure groups. Relative effect estimates will be calculated comparing galcanezumab-exposed pregnant women with confirmed migraine to each of the comparison groups using regression analysis. Baseline covariates that remain unbalanced after propensity score adjustment will be adjusted for in the regression analysis. Given the low prevalence of cluster headache and its high male:female ratio, comparative analyses within the cluster headache cohort is not expected to be feasible and will not be conducted. If sample sizes allow, effect estimates will be stratified by five exposure windows: four months before pregnancy, during each trimester and throughout the pregnancy. Given that we will only be able to acquire approximately 40% of requested medical records (HealthCore, internal communication) and the incomplete capture by medical records of certain lifestyle risk factors, we will address missing covariate data using multiple imputation.

Sensitivity analyses, if sample sizes allow, will include analysis without imputation of the subset of patients for whom complete medical record data are available to confirm outcomes and restriction of the study population to women with at least 12 months of health plan eligibility prior to the start of pregnancy (as sample size allows). Other sensitivity analyses include extension of baseline covariate ascertainment for chronic conditions to 90 days after the estimated LMP so that pre-existing conditions documented at the first prenatal visit are captured and capturing galcanezumab and comparator medication dispensings that occurred only during pregnancy and during a pre-pregnancy washout period.

We propose using medical records to validate claims diagnoses for pre-eclampsia and major and minor congenital anomalies. Based on historical response rates, we expect medical records will be obtained for approximately 40% of the galcanezumab and the composite migraine prophylaxis group respectively. Records will be submitted to clinical experts for adjudication.

**Milestones**

The start of data collection will be 31 October 2020. Annual study reports will be provided in the periodic safety update report/periodic benefit-risk evaluation report (PSUR/PBRER) based on regulated timelines. A European Medicines Agency (EMA)-specific interim report will be provided to the EMA by 31 December 2022. An FDA-specific interim report will be provided to the FDA by 31 December 2024. A final report of study results will be submitted to the EMA by 31 December 2024 and the FDA by 31 December 2027.

# 5. Amendments and Updates

| Amendment or update number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| None | | | | |

# 6. Milestones

| Milestone | Planned date |
|---|---|
| Start of data collection (EMA/FDA) | 31 October 2020 |
| End of data collection (EMA) | 31 December 2023 |
| End of data collection (FDA) | 30 June 2026 |
| Annual reporting to regulatory agencies | To be provided annually with the PSUR starting 30 November 2019 |
| EMA Interim report | 31 December 2022 |
| FDA Interim report | 31 December 2024 |
| Registration in the European Union Post-authorisation studies (EU PAS) Register | 16 January 2019 |
| EMA Final report of study results | 31 December 2024 |
| FDA Final report of study results | 31 December 2027 |

# 7. Rationale and Background

Migraine is a recurrent headache disorder characterized by painful attacks lasting four to 72 hours and usually accompanied by other symptoms including nausea, vomiting, sensitivity to light and sound, and changes in vision [6]. It is a spectrum of illness, with clinical symptoms that vary along a continuum from episodic to chronic migraine. Episodic migraine is characterized by ≤14 headache days per month, while chronic migraine is characterized by 15 or more headache days per month, and is much less common than episodic migraine [7, 8].

Cluster headache is one of the most severe primary headache syndromes and is characterized by recurrent attacks of intense headaches on one side of the head, frequently associated with pain behind or around one eye, restlessness and agitation [9]. A cluster period generally lasts from six to 12 weeks and a single attack typically lasts between 15 minutes and three hours [10].Cluster headache has been associated with seasonal changes with higher incidence of attacks reported in the fall and spring [11]. The International Headache Society (IHS) classified cluster headache into two major temporal types: episodic (85–90%) and chronic (10–15%). The prevalence of overall cluster headache is approximately 1% and it mostly affects men with overall male-to-female ratio of four to one [12].

Galcanezumab is a humanized monoclonal antibody that selectively binds to calcitonin gene-related peptide (CGRP) and inhibits its activity. Elevated blood concentrations of CGRP have been associated with migraine or cluster headache attacks [13]. Three placebo-controlled Phase 3 clinical trials demonstrated a reduction in the number of monthly migraine headache days for galcanezumab in patients with episodic migraine (EVOLVE-1 and EVOLVE-2) and patients with chronic migraine (REGAIN) [14] . Another placebo-controlled Phase 3 study of patients with episodic cluster headache also demonstrated a significant reduction of weekly cluster headache attacks from baseline across weeks 1-3 comparing galcanezumab with placebo; results were presented at the 2018 American Headache Society annual meeting. Emgality™ (galcanezumab), a once-monthly, subcutaneous 120 mg injection, which has a half-life of 27 days, has received approval from the Food and Drug Administration (FDA) for the preventive treatment of migraine in adults on 27 September 2018 and a marketing authorization from European Commission in adults who have at least four migraine days per month, on 14 November 2018.

As is standard, pregnant women were not included in the clinical development program; however, a small number of pregnancies occurred in women treated with galcanezumab in clinical trials. The current nonclinical data and the low number of pregnancy exposures in humans are insufficient to draw conclusions about the effect or safety of galcanezumab exposure during human pregnancy. However, migraine prevalence is highest in women aged 18 to 49 years [7] during typical childbearing years. There is often a medical need for prophylactic treatment of migraine during pregnancy, with treatment decisions based on clinical judgement of the benefits and the potential harms [1]. It is anticipated that given the treated patient population and the long half-life of galcanezumab, exposure during pregnancy will occur in the post-authorization setting and thus, further study is warranted in this setting.

Women with migraine have been reported to be at increased risk of developing hypertensive disorders of pregnancy such as pre-eclampsia compared to women without migraine [15, 16]. In the migraine population, more severe migraine is associated with increased prevalence of cardiovascular comorbidity, as well as anxiety and depression [17]. Therefore, when examining the potential adverse pregnancy outcomes, there should be careful selection of comparison populations of women with migraine treated with prophylactic migraine medication in order to reduce confounding by migraine severity or comorbidities.

The proposed post-authorization safety study will actively monitor exposure to galcanezumab during pregnancy in women with migraine and cluster headache and study the incidence of pregnancy outcomes..

# 8. Research Question and Objectives

The primary objectives of this study are to:

- Monitor and describe exposure to galcanezumab during pregnancy in women with migraine or cluster headache.
- Monitor and describe exposure to other medications indicated for migraine prophylaxis during pregnancy in women with migraine.
- Describe the incidence of pregnancy, maternal and infant outcomes among pregnant women exposed to galcanezumab for migraine and cluster headache, or other medications for migraine in routine clinical practice in the United States (US).

The pregnancy, maternal and fetal/infant outcomes of interest include:

(1) Pregnancy outcomes: recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery.
(2) Maternal outcomes: hypertension during pregnancy, and pre-eclampsia.
(3) Fetal/infant outcomes: small for gestational age, major and minor congenital malformations.

The secondary objective, if a sufficient number of women with migraine exposed to galcanezumab during pregnancy and infants linked to the exposed pregnancies are identified, is to conduct comparative safety analyses of maternal, pregnancy and fetal/infant outcomes between pregnant women with migraine exposed to galcanezumab with the following comparator groups:

(1) Women with migraine with active exposure to any of a composite of other migraine prophylaxis medications during pregnancy.:

(2) Women diagnosed with migraine who were not exposed to migraine prophylaxis during pregnancy:
    a. Pregnant women with migraine treated with triptans.
    b. Pregnant women with migraine and prior history of CGRP-inhibitor use, who were not dispensed a CGRP-inhibitor at least four months prior to the start of pregnancy. A four-month pre-pregnancy interval has been specified to account for the long elimination half-life of galcanezumab.
(3) A population of commercially insured pregnant women without migraine diagnosis and without exposure to galcanezumab.

# 9. Research Methods

## 9.1. Study design

This is a cohort study using secondary data will include two phases:

**Phase 1: Galcanezumab uptake monitoring and descriptive analysis**

- Monitor the total number of pregnant women exposed to galcanezumab or other migraine prophylaxis medications and describe the maternal (hypertension during pregnancy, and pre-eclampsia), pregnancy (recognized spontaneous abortions, stillbirths, elective terminations, preterm delivery) and fetal/infant (small for gestational age, major congenital malformations and minor congenital anomalies (up to 12 months of age) outcomes among exposed pregnant women and their infants. Numbers and percentages of patients and outcomes will be presented. Additionally, only among the galcanezumab exposed cohorts, these results will be stratified and reported and among cohorts/sub-cohorts defined by diagnosis/treatment of migraine or cluster headache. (See Section 9.2.2.1. Phase 1 Descriptive Analysis).
- Describe patient characteristics including demographics, comorbidities, concomitant medication use and health care utilization among pregnant women exposed to galcanezumab or other migraine prophylaxis medications. Additionally, only among the galcanezumab exposed cohort, these results will be stratified and reported and among cohorts/sub-cohorts defined by diagnosis/treatment of migraine or cluster headache. (See Section 9.2.2.1. Phase 1 Descriptive Analysis).
- Estimate incidence rates or birth prevalence for recognized spontaneous abortions, stillbirths, elective terminations, preterm delivery, small for gestational age, and major and minor congenital anomalies among infants of pregnant women exposed to galcanezumab or other migraine prophylaxis medications. Additionally, only among the galcanezumab exposed cohorts, these results will be stratified and reported and among cohorts/sub-cohorts defined by diagnosis/treatment of migraine or cluster headache. (See Section 9.2.2.1. Phase 1 Descriptive Analysis).
- Uptake monitoring will occur annually for 2020-2026. After each monitoring cycle, overall patient accrual will be compared against the target sample sizes estimated to detect at least a two-fold difference in the risks of pre-eclampsia for and major congenital malformations with at least 80% power to determine feasibility for Phase 2.

**Phase 2: Comparative analyses** If the target sample size (See Section 9.4 Study Size) is reached, we will conduct comparative analyses for specific outcomes, comparing galcanezumab-exposed pregnant patients with pregnant patients with confirmation of migraine diagnosis in the comparator groups (See Section 9.2.2.2. Phase 2 Comparative Analyses).

- Administrative data will be supplemented with medical record review to verify the timing of pregnancy, outcomes, and available covariates not captured in claims. We

will request supplemental medical record data for all patients but, based on previous experience, expect to obtain approximately 40% of requested records.
Propensity score adjusted incidence rates (IR) and incidence rate ratios (IRR), or birth prevalence rates and birth prevalence ratios with applicable 95% confidence interval (CI) will be presented as appropriate for each individual outcome.

## 9.2. Setting

This study will be conducted using longitudinal medical and pharmacy claims data from commercial health plan members across the US. All available data prior to the start of the pregnancy will be used to assess baseline characteristics. Claims will be utilized as the data source for exposure status, endpoints and covariates, if available. Medical records will be utilized to confirm endpoints and covariates that are questionably captured in claims (e.g. body mass index (BMI), smoking, alcohol use) for the galcanezumab exposed and active comparator cohorts.

### 9.2.1. Data Sources

Initial uptake monitoring will occur in the HealthCore Integrated Research Database (HIRD), a large administrative healthcare database maintained by HealthCore for use in health outcomes and pharmacoepidemiologic research. The HIRD is a broad, clinically rich, and geographically diverse data spectrum of longitudinal medical and pharmacy claims data from commercially-insured health plan members across the US. Member enrollment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data, and health care utilization may be tracked for health plan members in the database dating back to January 2006. As of July 2017, there are 48.1 million individuals with medical and pharmacy coverage who may be included for research using the HIRD. 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. In past studies involving linkage of mothers and their infants, approximately 70-75% of completed pregnancies could be connected to a qualifying infant. In cases where infant mother cannot be linked by subscriber identifier to her infant, it is likely that the infant was covered by the insurance plan of the other parent.

### 9.2.2. Study Population

#### 9.2.2.1 Phase 1: Descriptive Analysis

Criteria for inclusion or exclusion in the **Galcanezumab Cohort** as a cohort of patients meeting all the following inclusion criteria (Figure 1):

**Inclusion criteria**:

- Female sex;

- Age 13-55 years;
- At least one pregnancy code;
- At least one pharmacy dispensing or injection in a health care setting for galcanezumab at any time from four months prior to until the end of pregnancy (Section 9.2.3: Study Period) and
- Continuous medical and pharmacy coverage for at least 180 days prior to and including the index date. The index date is defined as the first day of pregnancy.

**Exclusion criteria:**

- Insufficient data to define the start of pregnancy (e.g., diagnosis or procedure indicating pregnancy without a documented outcome, see Section 9.2.3: Study Period).
- Patients with implausible values for age or sex. In most studies using the HIRD, less than one percent of cohort members are excluded for these reasons.
- Exposed to other CGRP-inhibitor medications from four months prior to the start of pregnancy through delivery, because these medications may share class effects with galcanezumab.

These criteria aim to ensure that the included data represent women with potential exposure during pregnancy with adequate data availability to establish baseline covariates. In administrative data, infants are linked to the mother, in part, by a family identifier. If billing codes related to the delivery of an infant appear on the administrative record of a five-year-old or 65-year-old, it is likely that the record is for a sibling or grandparent respectively, rather than for the mother. Limiting the age of the study subjects improves the linkage algorithm and reduces the likelihood that a family member is incorrectly identified as the mother. Likewise, exclusion of individuals with both male and female sex recorded aims to avoid inclusion of individuals for whom claims data from multiple individuals have been mixed.

From the **Galcanezumab Cohort**, three additional cohorts meeting all the following criteria will be created as follows:

- **Galcanezumab Migraine Cohort**:
  - No diagnosis of cluster headache on and before the index date.
  - A diagnosis of migraine or a dispensing of triptans on and before the index date.
- **Galcanezumab Cluster Headache Cohort**:
  - A diagnosis of cluster headache on and before the index date.
- **Galcanezumab Cohort with Unknown Indications:**
  - No diagnosis of cluster headache, no diagnosis of migraine, and no dispensing of triptans on and before the index date.

For women meeting the inclusion and exclusion criteria defined above, we will also identify linked infants who are captured in the HIRD by requiring that the infant share the mother's subscriber identification number and have a date of birth within 30 days of the recorded delivery date. We will also explore the performance of alternative linking strategies in the event that

subscriber identification numbers are unavailable. The number of patients meeting each criterion will be provided for each attrition step. The numbers for each outcome (see Section 9.3.2: Outcomes) will be provided for the mothers and their linked infants who are eligible for the Phase 2 cohort.

Criteria for inclusion or exclusion in the **Composite Prophylactic Migraine Medication** comparator group as a cohort of patients meeting all the following criteria (Figure 1):

**Inclusion criteria**:

- Female sex;
- Age 13-55 years;
- At least one pregnancy code;
- A diagnosis of migraine or a dispensing of triptans on and before the index date;
- At least one pharmacy dispensing for amitriptyline, nortriptyline, , venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, or nadolol during a period of time prior to and until the end of pregnancy (Section 9.2.3: Study Period) (The exposure window prior to pregnancy will be determined by calculating the median days between claims to empirically ascertain how dispensing patterns within the HIRD will affect the length of the washout period); and
- Continuous medical and pharmacy coverage for at least 180 days prior to and including the index date. The index date is defined as the first day of pregnancy.

**Exclusion criteria:**

- Insufficient data to define the start of pregnancy (e.g., diagnosis or procedure indicating pregnancy without a documented outcome, see Section 9.2.3: Study Period).
- Patients with implausible values for age or sex. In most studies using the HIRD, less than one percent of cohort members are excluded for these reasons.
- Exposed to CGRP-inhibitor medications from four months prior to the start of pregnancy through delivery, noting that these medications may share class effects with galcanezumab.

#### 9.2.2.2. Phase 2: Comparative Analyses

The evaluation of pregnancy, maternal and fetal/infant outcomes among galcanezumab exposed women with migraine and a comparator population is particularly challenging given the known associations of some prophylactic migraine medications with congenital malformations and other study outcomes. Concerns about channelling bias that may be associated with the use of other migraine medications and the risk of pregnancy outcomes associated with other disease states that share similar treatments further complicate the selection of a comparator group.

Therefore, we propose using the following comparator groups for the comparative analyses (Figure 2):

(1) Women with migraine exposed to any one of a composite migraine prophylaxis medications during pregnancy:
    a. Pregnant women treated during pregnancy with other medications used in migraine prophylaxis, including amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, and nadolol (Migraine prophylaxis cohort)
        - This composite migraine medication cohort mitigates confounding by indication by limiting the comparator group to those individuals who require treatment for migraine prophylaxis during pregnancy despite risks. The migraine prophylaxis cohort is heterogeneous and represents a variety of treatment modalities that may be used to manage severe migraine patients during pregnancy[18] (excepting CGRP-inhibitor use given the possibility of class effects). The inclusion of multiple medications allows for restriction of the cohort to the subset of patients treated with medications that are not associated with a given outcome as follows:
            1. Pregnancy outcomes (recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery): all medications will be used
            2. Maternal outcomes (hypertension during pregnancy, and pre-eclampsia): divalproex, topiramate, and valproate will be used
            3. Fetal/infant outcomes:
                a. Small for gestational age: all medications will be used
                b. Major and minor congenital malformations: amitriptyline, nortriptyline, and venlafaxine will be used

(2) Women diagnosed with migraine who were not exposed to migraine prophylaxis during pregnancy:
    a. Pregnant women with migraine treated with triptans (Triptan cohort)
        - This cohort ensures that women have migraine by requiring either a diagnosis of migraine and/or the use of a medication indicated for acute management, but does not include migraine prophylaxis medications. As such, it is expected that migraine severity may differ from the galcanezumab exposed. This is not expected to bias estimates for major congenital malformations where no association with either triptans or migraine severity has been described [19, 20]. It is possible that the groups will also differ with respect to use of other medications for acute management of migraine pain, such as opioids, which have been associated with malformations [21].

Analyses of pre-eclampsia and hypertension will be biased in a less predictable direction. Triptans are contraindicated in patients with underlying uncontrolled hypertension, angina and ischemic heart disease [22]. As a result, patients prescribed triptans might also appear to have a lower risk for adverse cardiovascular outcomes compared to those prescribed galcanezumab. Conversely, galcanezumab users may have more severe disease, which would increase the risk of these outcomes independently of medication use.

b. Pregnant women with migraine and prior history of CGRP-inhibitor use, who discontinued therapy 4 months or more prior to the start of pregnancy (Past CGRP cohort)
    - This cohort ensures that women are indicated for treatment with CGRP-inhibitors which have limited indications for use compared to other migraine prophylaxis medications. Migraine severity may differ between women who continue and those who discontinue medication use during pregnancy, which could impact the risk for pre-eclampsia and hypertension as described above. Assessment of congenital malformations is not known to be affected by differences in migraine severity.

3. A general population of pregnant women with commercial insurance who do not have any diagnoses of migraine or exposure to galcanezumab.
    - This cohort does not limit to women who are in the target population for galcanezumab and provides background incidence rates that (within the confines of propensity score adjusted analyses) are more similar to the general population. Because women with migraine are excluded from the comparator cohort, it will not be possible to determine whether any observed associations reflect effects of galcanezumab or migraine given intractable confounding.

The following study entry criteria will be applied to all cohorts for the comparative analyses.

**Inclusion criteria:**

- Female sex;
- Age 13-55 years;
- At least one pregnancy within the study period (Section 9.2.3: Study Period); and
- At least one diagnosis of migraine prior to or during pregnancy.

For infant outcomes, mother-infant pairs will further be limited to those where the infant date of birth within 30 days of date of delivery, there is a shared subscriber identifier between the mother and infant, and the infant is enrolled in a health plan for at least 90 days with enrollment starting within 30 days after birth. Although this would potentially exclude infants whose malformations are fatal (e.g., anencephaly), evidence of malformation from a mother's record will be accepted in instances of infant death.

**Exclusion criteria:**

- Insufficient data to define the start of pregnancy (e.g., diagnosis or procedure indicating pregnancy without a documented outcome, see Section 9.2.3: Study Period);
- Less than six months of continuous health plan eligibility available prior to the start of pregnancy;
- Exposure to CGRP-inhibitor medications other than galcanezumab from four months prior to the start of pregnancy through delivery, noting that these medications may share class effects with galcanezumab; and
- For analyses of malformations, mother-infant pairs with exposure to known severely teratogenic medications within three months before or during pregnancy (extended to six months for drugs with a long half-life (e.g., acitretin)).

Additional cohort-specific considerations:

Galcanezumab exposed cohort:

- Inclusion: A qualified exposed pregnancy must have at least one dispensing or administration of galcanezumab, four months prior to or at any time during pregnancy (Section 9.2.3: Study Period).
- Exclusion: When conducting comparative analysis with the population of pregnant women with commercial insurance and without a migraine diagnosis, a qualified exposed pregnancy must have no migraine diagnosis.

Composite migraine prophylaxis exposed cohort:

- Inclusion: A qualified pregnancy must have at least one dispensing of at least one of the following migraine prophylaxis medications: amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, or nadolol at any time during pregnancy or a pre-pregnancy period (to be determined using claims data) (Section 9.2.3: Study Period).
- Exclusion: Exposure to galcanezumab from four months prior to the start of pregnancy through delivery, and drug-specific exclusions for co-morbidities that are indications other than migraine.

Triptan cohort:

- Inclusion: A qualified exposed pregnancy must have at least one dispensing of triptans, during pregnancy or during a pre-pregnancy period (to be determined in a similar manner as the prophylactic migraine medication cohort) (Section 9.2.3: Study Period).
- Exclusion:
  - Exposure to galcanezumab from four months prior to the start of pregnancy through delivery.
  - A pregnancy with at least one dispensing of any other migraine prophylaxis during four months prior to or at any time during pregnancy (Section 9.2.3: Study Period).

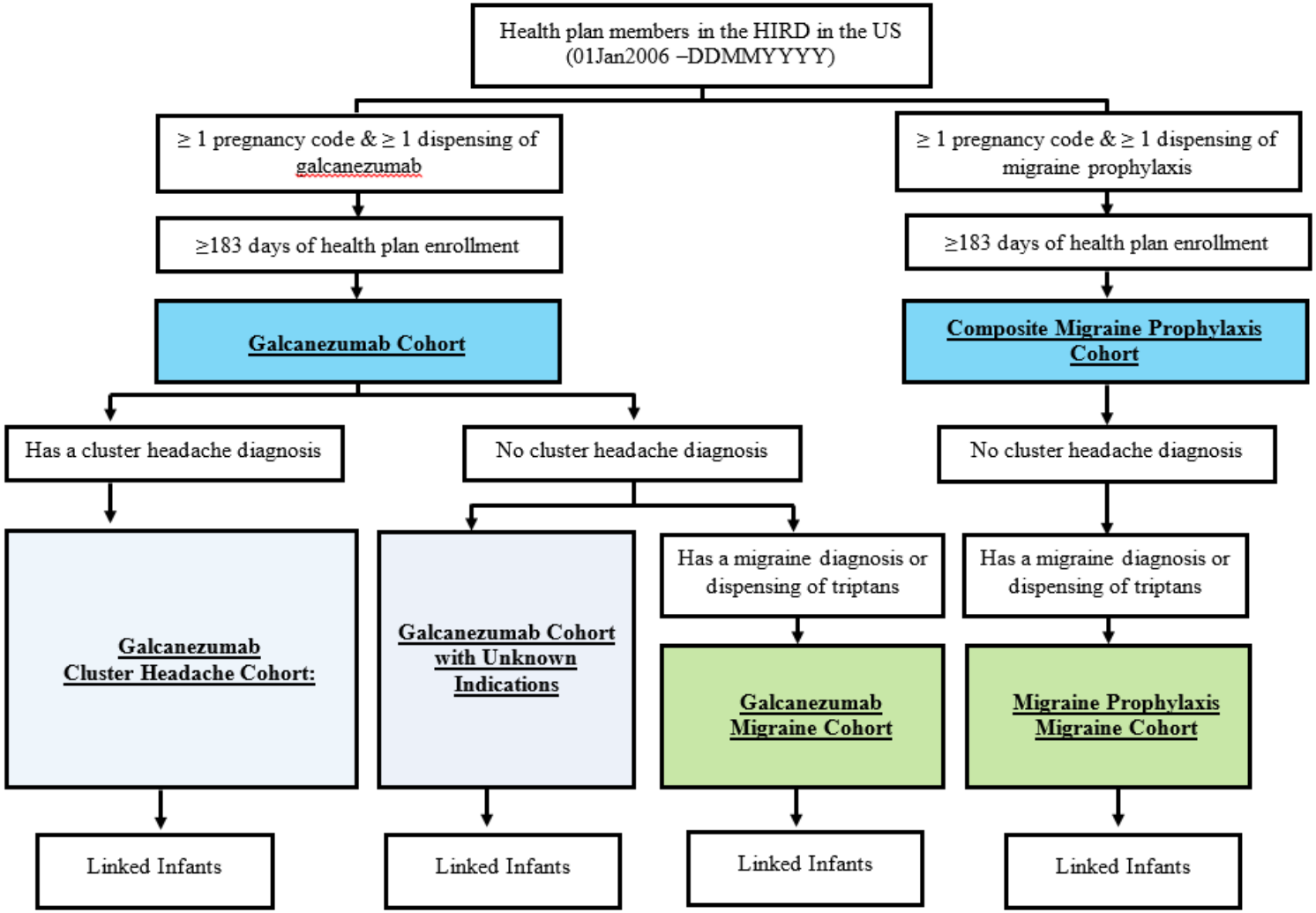
- Note: When comparing the galcanezumab and triptan cohorts, galcanezumab users with triptan use during the four months prior to or during pregnancy will also be excluded.

Past CGRP Cohort:

- Inclusion: A qualified pregnancy must have past exposure to CGRP-inhibitors discontinued at least four months prior to the start of pregnancy and no exposure to prophylactic migraine medications (including galcanezumab).

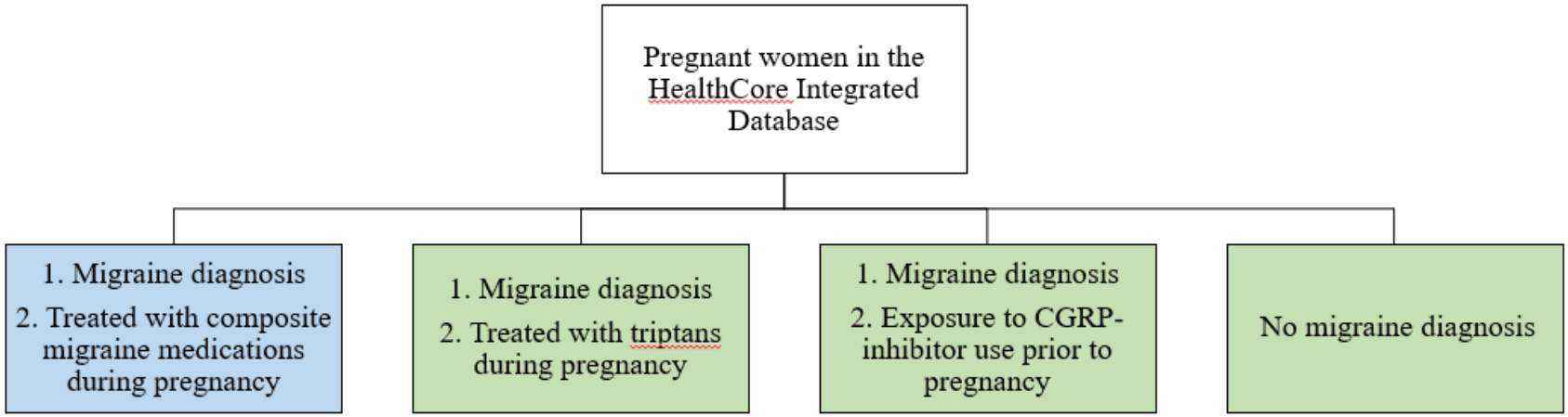
For the Phase 2 cohorts, all patients meeting these criteria will be included in the main analysis, where we will use multiple imputation to address key missing variables not captured due to absent or incomplete medical record data. We will also conduct a sensitivity analysis that will be limited to those mothers and their linked infants for whom at least one medical record was successfully obtained and abstracted to confirm pregnancy timing, outcomes, and covariates not otherwise available in claims. The number of patients excluded in this sensitivity analysis due to inability to obtain medical records and their characteristics based on the administrative claims will also be described. Additional details will be provided in the Statistical Analysis Plan (SAP).

**Figure 1. Flow diagram showing the composition of the study population for Phase 1**




*HIRD = HealthCore Integrated Research Database, US = United States*

**Figure 2. Diagram showing the composition of the comparator study populations for Phase 2**




*CGRP = Calcitonin Gene-Related Peptide*

### 9.2.3. Study Period

**Phase 1:**

Galcanezumab was approved by the FDA on 27 September 2018. Therefore, the planned intake period will start on 28 September 2018. Phase 1 will continue until the target number of mother/infant pairs exposed to galcanezumab are accrued or until the end of the study period, 31 December 2023 for final submission to the European Medicines Agency (EMA) on 31 December 2024 and 30 June 2026 for final submission to the FDA on 31 December 2027.

**Phase 2:**

The comparative analyses for Phase 2 will be initiated once the target number of galcanezumab exposed mother/infant pairs are accrued and will continue as feasible.

Because the comparator groups should be larger than the galcanezumab group, we do not anticipate difficulty identifying a sufficient number of comparators. If, however, the number of mother-infant comparator pairs is not sufficient, all available claims data dating back to 2006 will be used to identify a sufficient number of comparators. Calendar year will be included as a covariate so that we may describe the time period when patients are accrued. The time period limited to the interval when galcanezumab was on the market is preferred as a primary analysis given the possibility of underlying secular trends and changes in technology and healthcare standards through which malformations may be detected and treated.

Because administrative claims data do not specifically identify the date of the last menstrual period (LMP), we will identify LMP using a two-phased approach. In the first phase, the following broad criteria will be used to assign the start of pregnancy in claims-based screening:

- Where a gestational age-specific code is recorded at infant delivery, we will subtract the specified number of weeks from the delivery date to establish the start of pregnancy. Given that these codes have been required for reimbursement since late 2018, they are expected to be commonly used.
- Where a gestational age-specific code is not used, the following will apply.
    - For women with documentation of a full-term delivery without a specified gestational age, we will consider the start of pregnancy to have occurred 42 weeks prior to the date of delivery.
    - For women with documentation of a pre-term delivery without a specified gestational age, we will consider the start of pregnancy to have occurred 36 weeks prior to the date of delivery.
    - For women with documentation of a spontaneous or elective termination, we will consider the start of pregnancy to have occurred 20 weeks prior to the date of the pregnancy outcome.

A similar approach to identify the start of pregnancy has been applied in past studies for full-term and preterm deliveries [2, 6, 23]. Although spontaneous or elective terminations are less described in administrative claims data, we selected this threshold as 20 weeks defines the transition from spontaneous abortion to stillbirth [24].

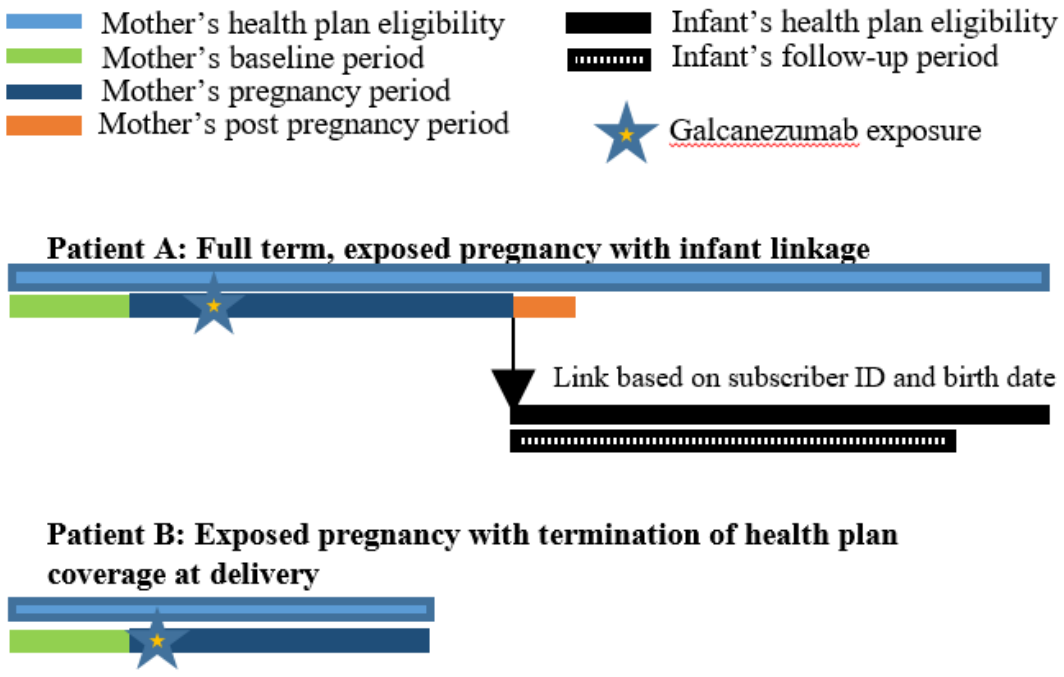
Where a pregnancy outcome is not identified in the claims, the pregnancy window cannot be defined. The number of these possibly exposed pregnancies will be tabulated for descriptive purposes; however, they will not be included in the analysis.

For women who are exposed during pregnancy or prior to the start of pregnancy, the study period will be divided into the pre-pregnancy baseline period (minimum duration of six months), the pregnancy period (overall and by trimester), and the six-week post pregnancy period to assess baseline covariates, pregnancy exposures, and post-partum events. For infants who are successfully linked to their mother (see Section 9.2.2: Study Population), follow-up will continue until either the earlier of the end of the infant's continuous health plan eligibility or age 12 months.

Two examples of study period ascertainment are shown in Figure 3.

- Patient A is followed from the start of her continuous health plan eligibility through her full-term pregnancy and six weeks post-partum. Her linked infant is then followed until age one year.
- Patient B is followed from the start of her continuous health plan eligibility through her pre-term pregnancy, however her health plan eligibility segment ends at the delivery date/end of the pregnancy period (which could be attributable to either a transfer to a spouse's insurance coverage, job loss, death during delivery, etc.). As such, her six-week post-partum period is not available for analysis, however her pregnancy outcomes would be included in the analyses. Her infant is not identifiable and is therefore not captured in the cohort for analysis.

**Figure 3. Observation periods**



## 9.3. Variables

### 9.3.1. Exposures

Exposure to galcanezumab or comparator medications (e.g., triptans or composite migraine prophylaxis medications) will be ascertained based on outpatient pharmacy dispensings and based on injections that occur in a health care setting. Specific applicable codes will be detailed in a separate SAP. We will define an exposure to galcanezumab as a dispensing or administration of a study drug that occurs during the four months prior to the start of pregnancy or within the pregnancy period (see Section 9.2.3: Study Period), which will be estimated based on the administrative claims and confirmed by medical record review in Phase 2. A four-month pre-pregnancy interval has been specified to account for the elimination half-life of galcanezumab.

For women in the composite migraine prophylaxis group, exposure will be defined as a dispensing during pregnancy or a pre-pregnancy exposure period. The exposure window prior to pregnancy will be determined by calculating the mean and median of days between dispensings, allowing us to empirically ascertain how dispensing patterns within the HIRD will affect the length of the washout period for these medications. This will be done with the aim of reducing exposure misclassification for these medications.

For women in the comparator group with prior exposure to CGRP inhibitors, evidence of discontinuation of migraine prophylaxis medications will be ascertained by evidence of dispensings followed by the absence of any dispensings for four months prior to pregnancy until the end of pregnancy.

### 9.3.2. Outcomes

The study outcomes listed below will be analyzed, with each considered as a separate entity. In Phase 1, administrative claims data will be used to identify each outcome on the basis of International Classification of Disease, 10$^{th}$ Revision (ICD-10) diagnosis and procedure, Common Procedural Terminology (CPT), and Health Insurance Portability and Accountability Act Codes (HCPCS), which will be detailed in a separate SAP. In Phase 2, medical records will be sought for each claims-identified outcome of pre-eclampsia, and major and minor congenital anomalies, noting that any outcome not captured in the claims data that is identified during medical record review will be counted as a confirmed outcome. Outcomes identified in claims where medical records are not available will be classified as unconfirmed outcomes.

Criteria to ascertain each individual malformation will be agreed upon in consultation with clinical 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. For these challenging outcomes, two clinicians 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.

- Outcomes will include the following as identified from the mother's medical claims:
    - Recognized spontaneous abortions
    - Stillbirths
    - Elective terminations
    - Hypertension during pregnancy
    - Preeclampsia
- Outcomes that will be identified based on medical claims from either the mother or her linked infant within one month of the end of the exposed pregnancy (which allows for capture of data not recorded at the initial hospitalization):
    - Preterm delivery
    - Small for gestational age infants
- Infant outcomes will include the following as identified on either infant medical claims during the first year of life unless otherwise specified (where linked) or maternal claims between the start of pregnancy and the end of the six-week post-partum period. Maternal claims will be used to account for the possibility of infant death prior to establishing a separate member identifier for the infant and occasional mixing of maternal and infant claims in the first few weeks of an infant's life.
- Major and minor congenital anomalies, both individually and as a composite, including the conditions listed in Annex 3: Congenital Malformations:
    - A composite of all major congenital malformations is the primary endpoint for the cohort study. A table will be provided that shows all defects, defects by class, and within classes where defects are identified, by specific defect.
    - Minor malformations will also be assessed both as a composite and individually.
    - For analysis of major and minor congenital malformations, we will exclude the following infants:
        - Syndromic or chromosomal cause (e.g., Trisomy 13, Trisomy 18, Trisomy 21, other trisomies and monosomies, Turner's syndrome, other chromosomal anomalies, and other specified congenital malformation syndromes affecting multiple systems).
        - Infants with prenatal exposure to serious teratogens, including thalidomide and retinoids. Other medications recommended by consulting clinical experts as exclusions or factors to be considered in statistical adjustment will be defined in the SAP.

### 9.3.3. Covariates

In the Phase 1 study, the variables listed below will be defined for mothers included in the cohort. Operational definitions and codes will be defined in the SAP. All variables will be identified during the pre-pregnancy baseline period unless otherwise specified.

- Demographic and general characteristics:
  - Age (years) at start of pregnancy
  - US region of residence
  - Duration of health plan eligibility prior to pregnancy
  - Calendar year of pregnancy outcome
- Clinical characteristics will be identified based on ICD-10 diagnosis codes:
  - Anxiety
  - Bipolar disorder
  - Dependence (alcohol and substance use)
  - Depression
  - Hyperlipidemia
  - Diabetes I & II
  - Hypertension
  - Malignancy
  - Overweight and obesity, as available in claims
  - Smoking, as available in claims
  - History of cardiovascular (CV) diseases:
    - Myocardial infarction (MI)
    - Transient ischemic attack (TIA)
    - Ischaemic stroke
    - Ischaemic heart disease
    - Angina
    - Heart failure
    - Cardiac arrhythmia
    - Haemorrhagic stroke
    - Peripheral vascular disease
  - On- and off-label indications other than migraine for eligible antidepressants including depression, anxiety disorder, panic disorder, and obsessive compulsive disorder
  - Migraine type (e.g., with vs. without aura) and severity (with vs. without intractable pain)
  - Cluster headache type and severity (with vs. without intractable pain)
  - 25 most frequently occurring diagnoses recorded (for descriptive analyses)
- Medication use (defined separately in the six months prior to and during pregnancy) will be identified based on Generic Product Identifier (GPI) or HCPCS codes as applicable:

  - Use of medications of known teratogenic potential (note: excludes the mother-infant pair from analysis of major and minor congenital anomalies):

        - Retinoids
        - Thalidomide
        - Others will be added based on consultation with clinical experts
    - Other medication use:
        - Prophylactic migraine drugs
        - Prophylactic cluster headache drugs
        - Acute migraine drugs
        - Acute cluster headache drugs
        - Analgesics (e.g. opioids, non-steroidal anti-inflammatory drugs (NSAIDs))
        - Antidepressants
        - Anti-epileptic medications
        - Antipsychotics
        - Antihypertensive medications
        - Antiplatelet agents
        - Anticoagulants
    - 25 most frequently dispensed medication classes (for descriptive analyses)
- Health care utilization (separately within the six months prior to and during pregnancy):
    - Count of office visits, emergency department visits, and hospitalizations
    - Number of distinct medications used
    - Specialty of study drug prescriber, as available
    - Maternal morbidity index [25]

The following will be defined for linked infants during the 12 months after birth.

- Demographic characteristics:
    - Infant sex
    - US region of residence
    - Duration of health plan eligibility after birth
- Clinical characteristics:
    - 25 most frequently occurring diagnoses recorded
- Medication use:
    - 25 most frequently occurring medication classes used
- Health care utilization:
    - Count of office visits, emergency department visits, and hospitalizations
    - Number of distinct medications used

In Phase 2, additional covariate data will be ascertained based on medical record review.

- Maternal characteristics:
    - Race/ethnicity
    - Relevant family history
    - Relevant obstetric history, including parity and past pregnancy outcomes
    - Body mass index
    - Smoking status

  - Alcohol use
  - Use of prenatal vitamins and supplements
  - Use of over-the-counter medications
- Infant characteristics:
  - Race/ethnicity
  - Relevant family history
  - Birth weight
  - Gestational age

## 9.4. Study Size

The available number of exposed pregnancies will depend on the uptake of galcanezumab in the US among pregnant women. Comparative analyses will be conducted when sufficient migraine patients exposed to galcanezumab and comparator migraine patients are accrued to detect at least a two-fold difference in the risk of pre-eclampsia with at least 80% power.

Fetal/Infant Outcome:

The outcome of major congenital anomalies occurs in approximately 3% of births. If we use a 4:1 match ratio of comparator: galcanezumab and a z-alpha of 1.96, we would have 80% power to detect a relative risk of 2.00 with about 430 pairs of galcanezumab exposed pregnant women and matched infants. A target of 430 galcanezumab matched pairs and 1,800 comparators gives a total study size of about 2,230 linked pregnant women and infant pairs.

Maternal Outcome:

Assuming that pre-eclampsia occurs in approximately 3% of pregnancies in the general population, a 4:1 ratio of comparator: galcanezumab, and a z-alpha of 1.96, we would have 80% power to detect a relative risk of 2.00 with 430 galcanezumab-treated pregnant women and approximately 1,800 unexposed pregnant women.

Table 1 describes the minimum detectable risk ratios for the target sample sized (430 galcanezumab-treated pregnant women and 1,800 unexposed pregnant women) based on the maternal outcome of pre-eclampsia.

Based on study size calculations and outcomes of pre-eclampsia and major and minor congenital anomalies, we estimate the study will identify and seek medical records for approximately 300 cases (allowing for 200 cases for major congenital malformations and 100 cases of pre-eclampsia).

**Table 1: Minimum detectable risk ratio for study outcomes**

| Outcome | Estimated prevalence | Minimum detectable risk ratio with 430 galcanezumab-exposed subjects and 80% power and 4:1 match ratio |
|---|---|---|
| Major malformations | 3% | 2.00 |
| Hypertension in pregnancy | 4% | 1.83 |
| Preeclampsia | 3% | 2.00 |
| Recognized spontaneous abortions | 20% | 1.31 |
| Stillbirths | 1% | 2.89 |
| Elective terminations | 17% | 1.35 |
| Preterm delivery | 10% | 1.49 |
| Small for gestational age infants | 9% | 1.52 |

## 9.5. Data Management

Datasets and analytic programs will be kept on a secure server and archived per HealthCore record retention procedures. Full details concerning data security and quality assurance procedures will be captured in the SAP.

## 9.6. Data Analysis

### 9.6.1. Descriptive Analysis for Primary Objectives

In Phase 1, the number of women with prenatal exposure to galcanezumab and maternal and infant outcomes will be provided as specified in Section 9.2.2: Study Population. We will describe all the women by reporting the number and percentage in each cohort for all of the demographic, clinical, treatment and utilization characteristics described in Section 9.3.3: Covariates. The number of observations, mean, standard deviation, median, interquartile range, and range will be presented for continuous variables, and the number and percent of patients in each category will be presented for categorical variables.

We anticipate that missing data may arise where medical record confirmation is not possible. For example, a facility may refuse to provide the requested record, or the record may not contain a key piece of information required. In the main analysis, we will use a multiple imputation approach in which we will leverage the non-missing data to estimate the true value of certain missing variables. This will allow us to retain patients with valuable partial information by using their known variables to model and assign values of missing variables. We will also conduct a complete case analysis including only those patients with medical record data available and

describe patients who met all inclusion and exclusion criteria for whom at least one medical record could not be obtained.

For each outcome (see Section 9.3.2 Outcomes), we will describe either the IR (calculated as the number of events divided by the person-time at risk) or the birth prevalence (calculated as the number of events divided by the number of births). The applicable estimate will vary by outcome; however, each will be presented with 95% CI. Stratified outcome categories will be shown only where there is at least one individual meeting the applicable outcome definition.

### 9.6.2. Propensity Score-Adjusted Comparative Analyses

In Phase 2, if patient accrual reaches the target sample size, we will estimate IRR or birth prevalence ratios (as applicable) and their 95% CIs will be calculated comparing galcanezumab-exposed pregnancies versus other comparator groups. To control for confounding by indication, we will construct exposure propensity scores from applicable baseline characteristics (e.g., excluding the 25 most frequently occurring diagnoses and medication used only to describe the cohort). The propensity score is the predicted probability of being assigned to galcanezumab conditional on a set of observed covariates and will be generated using logistic regression. Distinct propensity scores will be estimated for each comparison group. Cohort members whose propensity score is outside the region of overlap will be trimmed and excluded from further analysis.

Estimates will be presented within the propensity score trimmed population and adjusted for propensity score decile. Given the low prevalence of cluster headache and the high male: female ratio, comparative analyses within the cluster headache cohort is not expected to feasible and therefore will not be conducted.

Baseline characteristics between the cohorts will be evaluated for imblanaces before any comparative outcome analyses begin. The study design will be modified if there is evidence that imblances will hinder the interpretation comparative analysis results. No outcome analyses will be performed until the baseline assessment has occurred and the study design is finalized.

### 9.6.3. Sensitivity Analyses

Planned sensitivity analyses will include:

(1) Depending on the frequency of outcomes, rates may be stratified by timing and duration of exposure. We will assess rates for all outcomes during the whole pregnancy and based on exposure by each trimester and possible exposures due to pre-pregnancy use and will discuss results in the context of their biologic plausibility. Although any duration of exposure will qualify a patient for inclusion in the study, we will describe the duration of exposure overall, during, or in the four months prior to the start of pregnancy, and during each trimester.
(2) Restriction of the study population to women with at least 12 months of health plan eligibility prior to the start of pregnancy (as sample size allows).

(3) Extension of baseline covariate ascertainment for chronic conditions to 90 days after the estimated LMP so that pre-existing conditions documented at the first prenatal visit are captured.
(4) Capture of galcanezumab administrations and migraine prophylaxis dispensings that occurred only during pregnancy and not prior to LMP, without a washout period prior to the start of pregnancy.

Additional details of the planned analyses will be described in the SAP.

## 9.7. Quality Control

Full details of the quality control process for data collection, analysis, and reporting are captured in the SAP.

## 9.8. Limitations of the Research Methods

This study integrates a large claims database with medical record review to conduct safety analyses of galcanezumab. To control for confounding by indication, we selected women being treated with medications approved for the same indications as galcanezumab as comparators. Doing so enhances comparability on indication, and on unmeasured factors related to indication that may also be related to outcomes. In addition, medical history and healthcare utilization recorded in the claims data may be used to compute propensity scores to further enhance comparability. Despite these efforts, there is potential for residual confounding by covariates not captured in automated claims or medical records.

The main limitations relate to uncertainties regarding the numbers of subjects available to study for a new medication, and limitations inherent in database studies, including accuracy and specificity of codes used to identify outcomes. Migraine often improves during pregnancy, and women with migraine may be counselled to discontinue systemic treatments when planning or learning of a pregnancy, suggesting that utilization of galcanezumab may be low in this population. Also, uptake of a new product (plus the follow-up time necessary to observe events) will determine the time at which a sufficient study size for analysis will accrue in the database as discussed in Section 9.4: Study Size. Although a sample of outcomes will be validated, and timing of pregnancy will be verified by medical record review, exposure and outcome misclassification may both present issues in the Phase 2 cohort surveillance study. For example, we will rely on pharmacy dispensing data to determine whether patients used medications, however it is possible that medication was purchased but not used. Likewise, verification of outcomes in the administrative claims will be limited to those outcomes that can be identified in the medical record. For example, a spontaneous abortion early in pregnancy may never come to medical attention, and therefore our outcome is limited to those situations where the patient seeks medical care. Similarly, elective terminations may take place at private clinics and not billed to insurance. Descriptive and comparative analyses of these outcomes should be considered exploratory given the limitations of the claims data to capture outcomes that may not come to the attention of the healthcare provider associated with insurance health plan.

Not all of the outcomes of interest have been validated in administrative claims data, and the performance of ICD-10 codes, which have been used only since October 2015 in the US, has not been well characterized in this setting. As such, we expect that the number of outcomes identified via administrative claims in Phase 1 uptake monitoring will differ from the number of outcomes verified by medical record review in Phase 2 cohort surveillance. Although positive predictive value (PPV) and sensitivity of algorithms based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes have been studied for some outcomes, their performance has been mixed. For example, for major congenital malformations (MCMs), a recent HealthCore study found wide variation in the performance of algorithms. While the PPVs for algorithms that detected specific MCMs were generally very good (PPV>70%), hydrocephalus (47.40%) and several cardiac defects –including atrial septal defect (37.90%), conotruncal heart defects (68.00%), and pulmonary valve atresia (44.40%) – had lower PPVs [26].

For some outcomes, high PPV has been reported with mixed findings on sensitivity. For example, ICD-9-CM small for gestational age codes were recently assessed in the US Medicaid Analytic eXtract and were found to have high PPV (86%) but poor sensitivity (14.20%) [27]. Studies from the Danish National Registry of Patients found a PPV of 97.40% (95 confidence interval (CI) 92.70-99.50) for spontaneous abortion [28] and 91.10% (95% CI 88.6-93.0) for miscarriage during the second trimester (using ICD-10 codes), however, capture of the outcome is limited to those events with medical supervision, and code performance may not generalize to the US. Assessments of stillbirth from administrative datasets in New South Wales, Australia have identified PPVs of 75% (95% CI 59-91) and 89% (95% CI 76-100) [29]. Positive predictive value estimates for elective termination were not identified by literature review.

Although use of medical record confirmed cases and verification of pregnancy timing in Phase 2 present important strengths of the study, it should be recognized that it will not be possible to obtain medical records for all mothers and infants. In cases where a patient seeks care at an out of network provider, for example, the provider is not identifiable in the administrative claims data. In other cases, a facility may not honor the Institutional Review Board (IRB) waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization due to institutional policies and refuse to provide the requested medical record. There may also be cases where a medical record is provided that does not capture the requested history. Although every attempt will be made to obtain complete records for mothers and their infants as will be detailed in the MRP, incomplete capture of the cohort may affect generalizability if those for whom medical record data are unavailable or incomplete differ in important ways from those who can be included. Although the proposed use of multiple imputation as well as use of multiple approaches in keeping with European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidelines for handling of missing data will help us to better understand the impact of the missing information, differences between individuals with and without missing data will require careful review.

Our proposed approach begins with the composite endpoints, in part because these endpoints will achieve sufficient study size before their components. However, composite endpoints such as

major congenital anomalies include many specific endpoints, some of which cannot be identified accurately in claims data, some of which are likely not related to the exposure of interest, and some of which may be associated with the exposure of interest. Because inaccurately coded outcomes, unrelated outcomes, and associated outcomes are grouped together in the composite endpoint, the association between galcanezumab and a composite endpoint may be attenuated compared with the association for a specific endpoint. In other words, the effect of the outcome that is associated with galcanezumab may be partially masked by other conditions that are included in the outcome definition but not associated with galcanezumab use. If a component endpoint is elevated, however, the composite endpoint also will be elevated although to a lesser degree, due to this misclassification.

Elective termination illustrates this misclassification concern. Whereas terminations of interest are those where the termination was motivated by parental knowledge about fetal anomalies, for example, the overall endpoint of elective terminations will comprise these cases and many other more common reasons why a woman may choose to end her pregnancy. If termination due to fetal anomalies was associated with galcanezumab use, but the majority of elective terminations were not due to fetal anomalies and were not associated with galcanezumab use, the overall assessment of the relation between galcanezumab use and elective terminations could be null despite a possibly elevated rate ratio for one of the endpoint components. We will explore endpoint components to the best of our ability, however, random error will be greater for the specific component endpoints than the composite endpoint, and it may be overwhelming for rare events.

Further, there is some possibility that maternal risk factors identified in the medical record may be more carefully ascertained for infants with outcomes than for infants without outcomes. A diligent clinician may, for example, take a more thorough maternal history for an infant who is very ill than for an infant who is not. Likewise, a complicated or high risk pregnancy will have more clinician encounters and therefore more opportunities for information on lifestyle factors to be collected. We will address this through review of missingness of elements collected from medical record review, which will be captured in such a way that medical records where there was no comment on an item are clearly identifiable (e.g., separating history of smoking: stated that never smoked, versus no data on smoking were identified). The SAP will also include plans for quantitative bias analysis in which any concerning findings regarding differential capture of data will be systematically explored to determine their potential impact on study results.

## 9.9. Other Aspects

Not applicable.

# 10. Protection of Human Subjects

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

# 11. Management and Reporting of Adverse Events (AE) / Adverse Reactions (AR)

This is a non-interventional study based on secondary data use, and therefore no individual case safety report reporting is required. The protocol-defined AEs are specified in Section 9.3.2 Outcomes. All protocol-defined AEs collected will be summarized in the interim and final study report. No other AEs will be collected.

## 11.1. Product Complaints

When a condition related to the pre-filled syringe, pen, or autoinjector necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure, the serious outcome of "required intervention" will be assigned.

Lilly collects product complaints on investigational products and drug delivery systems used in medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

# 12. Plans for Disseminating and Communicating Study Results

This study will produce periodic reports that will be delivered to the FDA and the EMA.

Results from Phase 2 may be disseminated via presentation at scientific conferences and/or publication in peer-reviewed journals.

# 13. References


1. Cassina M, et al., *Migraine therapy during pregnancy and lactation.* Expert Opin Drug Saf, 2010. **9**(6): p. 937-948.
2. Mines, D., et al., *Topiramate use in pregnancy and the birth prevalence of oral clefts.* Pharmacoepidemiol Drug Saf, 2014. **23**(10): p. 1017-25.
3. A, B., Z. JP, and S. O, *Antidepressant use during pregnancy and the risk of major congenital malformations in a cohort of depressed pregnant women: an updated analysis of the Quebec Pregnancy Cohort.* BMJ, 2017. **7**(1).
4. Rynn L, C.J., Correa, A *Update on Overall Prevalence of Major Birth Defects --- Atlanta, Georgia, 1978--2005.* 2008. **57**: p. 1-5.
5. Anath, C., K. Keyes, and R. Wapner, *Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis.* BMJ, 2013. **347**.
6. Katsarava, Z., et al., *Defining the differences between episodic migraine and chronic migraine.* Curr Pain Headache Rep, 2012. **16**(1): p. 86-92.
7. Buse, D.C., et al., *Chronic migraine prevalence, disability, and sociodemographic factors: results from the American Migraine Prevalence and Prevention Study.* Headache, 2012. **52**(10): p. 1456-70.
8. Lipton, R.B., et al., *Migraine prevalence, disease burden, and the need for preventive therapy.* Neurology, 2007. **68**(5): p. 343-9.
9. Ashkenazi, A. and T. Schwedt, *Cluster headache--acute and prophylactic therapy.* Headache, 2011. **51**(2): p. 272-86.
10. Ettlin, D.A., *The International Classification of Headache Disorders, 3rd Edition.* Cephalalgia, 2013. **33**(9): p. 629-808.
11. Costa, A., et al., *The Neuropharmacology of Cluster Headache and other Trigeminal Autonomic Cephalalgias* Curr Neuropharmacol, 2015. **13**(3): p. 304-323.
12. Fischera, M., et al., *The incidence and prevalence of cluster headache: a meta-analysis of population-based studies.* Cephalalgia, 2008. **28**(6): p. 614-8.
13. Durham, P.L., *Inhibition of calcitonin gene-related peptide function: a promising strategy for treating migraine.* Headache, 2008. **48**(8): p. 1269-75.
14. Forderreuther, S., et al., *Preventive effects of galcanezumab in adult patients with episodic or chronic migraine are persistent: data from the phase 3, randomized, double-blind, placebo-controlled EVOLVE-1, EVOLVE-2, and REGAIN studies.* J Headache Pain, 2018. **19**(1): p. 121.
15. Banhidy F, et al., *Pregnancy complications and delivery outcomes in pregnant women with severe migraine.* Eur J Obstet Gynecol Reprod Biol, 2007. **134**(2): p. 157-163.
16. Facchinetti F, et al., *Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. .* Cephalalgia, 2009. **29**(3): p. 286-292.
17. Chen, Y.C., et al., *Comorbidity profiles of chronic migraine sufferers in a national database in Taiwan.* J Headache Pain, 2012. **13**(4): p. 311-9.
18. H, T., O. D, and H. A, *Migraine-preventive prescription patterns by physician specialty in ambulatory care settings in the United States.* Prev Med Rep, 2017. **9**: p. 62-67.
19. A, M., et al., *Pregnancy outcome following prenatal exposure to triptan medications: a meta-analysis.* Headache, 2015. **55**(4): p. 490-501.

20. K, S., et al., *Pregnancy outcome after anti-migraine triptan use: A prospective observational cohort study.* Cephalalgia, 2018. **38**(6): p. 1081-1092.
21. J, L., et al., *Maternal Use of Opioids During Pregnancy and Congenital Malformations: A Systematic Review.* Pediatrics, 2017. **139**(6).
22. M, A., D. A, and S. U, *Triptans Use for Migraine Headache among Nonelderly Adults with Cardiovascular Risk.* Pain Research and Treatment, 2016.
23. Cole, J.A., et al., *Bupropion in pregnancy and the prevalence of congenital malformations.* Pharmacoepidemiol Drug Saf, 2007. **16**(5): p. 474-84.
24. Statistics, N.C.f.H. *Fetal Deaths*. 2016 April 29, 2016]; Available from: http://www.cdc.gov/nchs/nvss/fetal_death.htm.
25. Bateman, B.T., et al., *Development of a comorbidity index for use in obstetric patients.* Obstet Gynecol, 2013. **122**(5): p. 957-65.
26. Everage N.J., E.D.B., Zhou L., Deshpande G., Holick C.N., Chan A., Mines D., *Positive Predictive Values of Algorithms for Ascertainment of Major Congenital Malformations in Administrative Databases.* Pharmacoepidemiology and Drug Safety, 2013. **22**(S1): p. 194.
27. Phiri, K., et al., *Accuracy of ICD-9-CM coding to identify small for gestational age newborns.* Pharmacoepidemiol Drug Saf, 2015. **24**(4): p. 381-8.
28. Lohse, S.R., et al., *Validation of spontaneous abortion diagnoses in the Danish National Registry of Patients.* Clin Epidemiol, 2010. **2**: p. 247-50.
29. Hure, A.J., et al., *Validity and reliability of stillbirth data using linked self-reported and administrative datasets.* J Epidemiol, 2015. **25**(1): p. 30-7.
30. A, C.-V., et al., *The Metropolitan Atlanta Congenital Defects Program: 35 years of birth defects surveillance at the Centers for Disease Control and Prevention.* Birth Defects Res A Clin Mol Teratol, 2003. **67**(9): p. 617-624.

# Annex 1. List of Standalone Documents

| No. | Document Reference No. | Date | Title |
|---|---|---|---|
| None | | | |

# Annex 2. ENCePP Checklist for Study Protocols

| |
|---|
| **Study title:** Observational Cohort Study of Exposure to Galcanezumab during Pregnancy among Women with Migraine |

| |
|---|
| **EU PAS Register® number: EUPAS27574** |

| **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) | ☒ | ☐ | ☐ | 6 |
| 1.1.4 Interim progress report(s) | ☒ | ☐ | ☐ | 6 |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

| |
|---|
| |

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|

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

| **Section 2: Research question** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 2.1 Does the formulation of the research question and objectives clearly explain: | | | | |
| 2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue) | ☒ | ☐ | ☐ | 7 |
| 2.1.2 The objective(s) of the study? | ☒ | ☐ | ☐ | |
| 2.1.3 The target population? (e.g. population or subgroup to whom the study results are intended to be generalised) | ☒ | ☐ | ☐ | |
| 2.1.4 Which formal hypothesis(-es) is (are) to be tested? | ☐ | ☐ | ☒ | |
| 2.1.5 If applicable, that there is no *a priori* hypothesis? | ☐ | ☐ | ☒ | |

Comments:

| |
|---|
| The protocol discusses research questions and study objectives. A full discussion of statistical methods, including formal hypothesis testing as applicable, will be included in the Statistical Analysis Plan. |

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design) | ☒ | ☐ | ☐ | 9 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 9 |
| 3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk) | ☒ | ☐ | ☐ | 9 |
| 3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, | ☒ | ☐ | ☐ | 9 |

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| hazard ratio, number needed to harm (NNH) per year) | | | | |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11 |

Comments:

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| |

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2 Is the planned study population defined in terms of: | | | | |
| 4.2.1 Study time period? | ☒ | ☐ | ☐ | 9.2 |
| 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 9.2 |
| 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 9.2 |
| 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 9.2 |
| 4.2.5 Duration of follow-up? | ☒ | ☐ | ☐ | 9.2 |
| 4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria) | ☒ | ☐ | ☐ | 9.2.2 |

Comments:

| |
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| |

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

| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 9.8 |
| 5.3 Is exposure classified according to time windows? (e.g. 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:

| |
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| |

| **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? | ☐ | ☐ | ☒ | |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.2 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 9.8 |
| 6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management) | ☐ | ☐ | ☒ | |

Comments:

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| |

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|

| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol describe how confounding will be addressed in the study? | ☒ | ☐ | ☐ | 9.6 |
| 7.1.1 Does the protocol address confounding by indication if applicable? | ☒ | ☐ | ☐ | 9.6 |
| 7.2 Does the protocol address: | | | | |
| 7.2.1 Selection biases (e.g. healthy user bias) | ☒ | ☐ | ☐ | 9.2.1 & 9.8 |
| 7.2.2 Information biases (e.g. misclassification of exposure and endpoints, time-related bias) | ☒ | ☐ | ☐ | 9.8 |
| 7.3 Does the protocol address the validity of the study covariates? | ☒ | ☐ | ☐ | 9.8 |

Comments:

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| **Section 8: Effect modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☒ | ☐ | ☐ | 9.2.2 |

Comments:

| |
|---|
| Full details of these analyses will be included in the Statistical Analysis Plan. |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of: | | | | |
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.3.2 |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1.3 Covariates? | ☒ | ☐ | ☐ | 9.3.3 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.3.2 |
| 9.2.3 Covariates? (e.g. 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? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.3.2 Outcomes? (e.g. 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 the linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☒ | ☐ | |

Comments:

| |
|---|
| Specific codes and the algorithm that links mothers and infants will be described in the Statistical Analysis Plan. |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 9.6 |
| 10.2 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.6 |
| 10.3 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.6.3 |
| 10.4 Does the plan describe methods for adjusting for confounding? | ☒ | ☐ | ☐ | 9.6 |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.5 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.2.2 & 9.6 |
| 10.6 Is sample size and/or statistical power estimated? | ☒ | ☐ | ☐ | 9.4 |

Comments:

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| |

| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.5 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | 9.7 |
| 11.3 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 12 |

Comments:

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|---|
| Full details concerning data security and quality assurance procedures will be captured in the Statistical Analysis Plan.<br><br>A review of all external reports and scientific disclosures is performed by internal groups that are independent of the study teams (Section 15 below). |

| **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 biases? | ☒ | ☐ | ☐ | 9.8 |
| 12.1.2 Information biases? | ☒ | ☐ | ☐ | 9.8 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☒ | ☐ | ☐ | 9.8 |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 9.8 |

Comments:

| |
|---|
| Although the current protocol discusses use of multiple approaches analyse and explore bias from missing data, additional discussion of bias analysis will be included in the Statistical Analysis Plan. |

| **Section 13: Ethical issues** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 13.1 Have requirements of Ethics Committee/Institutional Review Board been described? | ☒ | ☐ | ☐ | 10 |
| 13.2 Has any outcome of an ethical review procedure been addressed? | ☐ | ☐ | ☒ | |
| 13.3 Have data protection requirements been described? | ☐ | ☒ | ☐ | |

Comments:

| |
|---|
| Full details of data protection requirements will be described in a separate Statistical Analysis Plan. |

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

Comments:

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| |

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

| **Section 15: Plans for communication of study results** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 15.1 Are plans described for communicating study results (e.g. to regulatory authorities)? | ☒ | ☐ | ☐ | 12 |
| 15.2 Are plans described for disseminating study results externally, including publication? | ☒ | ☐ | ☐ | 12 |

Comments:

| |
|---|
| |

Name of the main author of the protocol: _____

Date: / /

Signature: _____

# Annex 3. Congenital Malformations[30]

- Congenital malformations of the nervous system
  - Anencephaly and similar malformations
  - Encephalocele
  - Microcephaly
  - Congenital hydrocephalus
  - Spina bifida
  - Other congenital malformations of spinal cord, brain or nervous system
- Congenital malformations of eye, ear, face and neck
  - Congenital malformations of eyelid, lacrimal apparatus and orbit
  - Anophthalmos, microphthalmos and macrophthalmos
  - Congenital malformations of eye
  - Congenital malformations of ear
  - Congenital malformations of face and neck (excluding oral cleft)
- Congenital malformations of the circulatory system
  - Congenital malformations of cardiac chambers and connections
  - Congenital malformations of cardiac septa
  - Congenital malformations of pulmonary and tricuspid valves
  - Congenital malformations of aortic and mitral valves
  - Other congenital malformations of heart
  - Congenital malformations of great arteries
  - Congenital malformations of great veins
  - Other congenital malformations of peripheral vascular system
  - Other congenital malformations of circulatory system
- Congenital malformations of the respiratory system
- Cleft lip and cleft palate
- Other congenital malformations of the digestive system
  - Congenital absence, atresia and stenosis of small or large intestine
  - Other congenital malformations of digestive system
- Congenital malformations of genital organs
  - Hypospadias
  - Other congenital malformations of genital organs
- Congenital malformations of the urinary system
  - Renal agenesis and other reduction defects of kidney
  - Cystic kidney disease
  - Congenital obstructive defects of renal pelvis and congenital malformations of ureter
  - Other congenital malformations of kidney or urinary system
- Congenital malformations and deformations of the musculoskeletal system
  - Congenital deformities of hip
  - Congenital deformities of feet

- Polydactyly/Syndactyly
- Reduction defects
- Other congenital musculoskeletal deformities
    - Other congenital malformations of limb(s)
    - Other congenital malformations of skull and face bones
    - Congenital malformations of spine and bony thorax
    - Osteochondrodysplasia with defects of growth of tubular bones and spine
    - Other osteochondrodysplasias
    - Congenital malformations of musculoskeletal system, not elsewhere classified

- Other congenital malformations
    - Congenital ichthyosis
    - Epidermolysis bullosa
    - Other congenital malformations of skin
    - Congenital malformations of breast
    - Other congenital malformations of integument
    - Phakomatoses, not elsewhere classified
    - Congenital malformation syndromes due to known exogenous causes, not elsewhere classified
    - Other congenital malformations, not elsewhere classified