PASS Information

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Product reference:	EU/1/18/1330
Procedure number:	EMEA/H/C/004648
Marketing authorisation holder(s):	Eli Lilly and Company
Joint PASS:	No
Research question and objectives:	The primary objective of this study is to compare the risk of (1) major congenital malformations, and (2) pre-eclampsia, among women with migraine who are treated with galcanezumab within 5 half-lives (135 days) before last menstrual period (LMP) or any time during pregnancy, to women included in the following comparator groups: • Primary comparator group: o Women with migraine treated with oral non-calcitonin gene-related peptide (CGRP)-antagonist medications for migraine prophylaxis within 5 half-lives before LMP or any time during pregnancy and with no use of CGRP-antagonist medications within 5 half-lives before LMP or any time during pregnancy. • Secondary comparator groups: o Women with migraine who were not exposed to migraine prophylaxis medications within 5 half-lives before LMP or any time during pregnancy, separately for: • Pregnant women with a migraine diagnosis or treatment with triptans any time before or during pregnancy. • Pregnant women who are treated with triptans within 5 half-lives before LMP or any time during pregnancy. • Pregnant women with a migraine diagnosis or treatment with triptans any time before or during pregnancy and prior history of nonoral CGRP-antagonist use, who were not dispensed a CGRP-antagonist at least 5 half-lives prior to LMP.

Approval Date: 15-Jun-2022 GMT

	○ Women without a migraine diagnosis, a cluster headache diagnosis, triptan use, or exposure to galcanezumab or other CGRP-antagonist medications any time before or during pregnancy. Secondary objectives are to: • Monitor exposure to galcanezumab during pregnancy in women with (1) migraine, (2) episodic cluster headache, and (3) neither migraine nor cluster headache to inform subsequent timing and feasibility of comparative analysis. • Conduct comparative safety analyses of secondary maternal, pregnancy, and fetal/infant outcomes between pregnant women with migraine exposed to galcanezumab with each of the aforementioned comparator groups. The secondary pregnancy, maternal and fetal/infant outcomes of interest include: ○ Pregnancy outcomes: recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery. ○ Maternal outcomes: hypertension during pregnancy and eclampsia. ○ Fetal/infant outcomes: small for gestational age, low birthweight, and minor congenital malformations. • Describe patient characteristics and occurrence of pregnancy, maternal and infant outcomes among women in the galcanezumab (separately for women with (1) migraine, (2) episodic cluster headache, and (3) neither migraine nor cluster headache) and comparator cohorts.
Country(-ies) of study:	United States
Authors:	PPD HealthCore, Inc. 123 Justison Street, Suite 200 Wilmington, DE 19801-5134, United States PPD PPD HealthCore, Inc. 123 Justison Street, Suite 200 Wilmington, DE 19801-5134, United States PPD

Marketing Authorisation Holder

Marketing authorisation holder (MAH)	Eli Lilly Nederland B.V., Papendorpseweg 83, 3528BJ Utrecht, The Netherlands
MAH contact person	Lilly Global Patient Safety Pharmacoepidemiologist

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2. List of Abbreviations

Abbreviation	Term
AE	adverse event
ATC	anatomical therapeutic chemical
BMI	body mass index
CGRP	calcitonin gene-related peptide
CI	confidence interval
CV	cardiovascular
DALY	disability-adjusted life year
EMA	European Medicines Agency
ERB	ethical review board
EU	European Union
FDA	Food and Drug Administration
HCPCS	Healthcare Common Procedure Coding System
HIRD	HealthCore Integrated Research Database
HRQoL	health-related quality of life
ICD-10	International Classification of Diseases, Tenth Revision
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
PAS	postauthorisation studies
PBRER	periodic benefit-risk evaluation report
PPV	positive predictive value
QALY	quality adjusted life years
SAP	statistical analysis plan

3. Responsible Parties

Eli Lilly Investigators:

PPD
Principal Investigator
Lilly Corporate Center, Indianapolis, IN 46285, United States
PPD

PPD
Lilly Corporate Center, Indianapolis, IN 46285, United States
PPD

HealthCore Investigators:

PPD
Principal Investigator
PPD HealthCore, Inc., Wilmington, DE 19801, United States
PPD

PPD
Principal Scientist
PPD HealthCore, Inc., Wilmington, DE 19801, United States
PPD

4. Abstract

Title

Observational Cohort Study of Exposure to Galcanezumab during Pregnancy Among Women with Migraine

Version 3.0

PPD HealthCore, Inc.

PPD HealthCore, Inc.

PPD HealthCore, Inc.

Rationale and background

Galcanezumab is a humanized monoclonal antibody that binds to CGRP and prevents its biological activity without blocking the CGRP receptor. Galcanezumab is approved for use in adults for the treatment of episodic cluster headache and preventative treatment of migraine by the US FDA and for the prophylactic treatment of migraine by the European Commission. 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 objective of this study is to compare the risk of (1) major congenital malformations, and (2) pre-eclampsia, among women with migraine who are treated with galcanezumab within 5 half-lives before LMP or any time during pregnancy to women included in the following comparator groups:

- Primary comparator group:
    - Women with migraine treated with oral non-CGRP-antagonist medications for migraine prophylaxis within 5 half-lives before LMP or any time during pregnancy with no use of CGRP-antagonist medications within 5 half-lives before LMP or any time during pregnancy.
- Secondary comparator groups:
    - Women with migraine who were not exposed to migraine prophylaxis medications during or within 5 half-lives before LMP, separately for:
        - Pregnant women with a migraine diagnosis or treatment with triptans any time before or during pregnancy.
        - Pregnant women who are treated with triptans within 5 half-lives before LMP or any time during pregnancy.

- Pregnant women with a migraine diagnosis or treatment with triptans any time before or during pregnancy and prior history of non-oral CGRP-antagonist use, who were not dispensed a CGRP-antagonist at least 5 half-lives prior to LMP.
- Women without a migraine diagnosis, a cluster headache diagnosis, triptan use, or exposure to galcanezumab or other CGRP-antagonist medications within 5 half-lives before LMP or any time during pregnancy.

Secondary objectives are to:

- Monitor exposure to galcanezumab during pregnancy in women with (1) migraine, (2) episodic cluster headache, and (3) neither migraine nor cluster headache to inform subsequent timing and feasibility of comparative analysis.
- Conduct comparative safety analyses of secondary maternal, pregnancy, and fetal/infant outcomes between pregnant women with migraine exposed to galcanezumab with each of the aforementioned comparator groups. Secondary pregnancy, maternal, and fetal/infant outcomes of interest include:
    - Pregnancy outcomes: recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery.
    - Maternal outcomes: hypertension during pregnancy and eclampsia.
    - Fetal/infant outcomes: small for gestational age, low birthweight, and minor congenital malformations.
- Describe patient characteristics and occurrence of pregnancy, maternal and infant outcomes among women in the galcanezumab (separately for women with (1) migraine, (2) episodic cluster headache, and (3) neither migraine nor cluster headache) and comparator cohorts.

Study design

This is a cohort study using secondary data from administrative commercial insurance claims and will include 2 phases:

- Phase 1: We will monitor and provide counts of pregnant women who are exposed to galcanezumab with (1) migraine, defined as at least 1 diagnosis of migraine or at least 1 dispensing of a triptan medication in patients with no cluster headache diagnosis, (2) episodic cluster headache (defined as at least 1 episodic or unspecified cluster headache diagnosis and no chronic cluster headache diagnosis), or (3) neither migraine nor cluster headache. Uptake monitoring will occur annually from 2020 through 2026. After each monitoring cycle, overall patient accrual will be compared against the target sample sizes estimated to detect at least a 2-fold difference in the risk of major congenital malformations with at least 80% power to determine feasibility for Phase 2. If by the 2024 interim report extrapolation from product uptake indicates that study size in 2026 will be below target, we will initiate a feasibility assessment to identify additional data sources for inclusion in the study in order to accrue sufficient numbers of subjects to fulfill study objectives and maintain study timeline. It is estimated that feasibility assessment can be completed and additional data sources enrolled within 2 years, thus enabling the study to adhere to timelines for completion of Phase 2 comparative analyses and submission of the final study report in December of 2027.
- Phase 2: Interim and final descriptive analyses will characterize the galcanezumab cohort (overall and stratified by (1) migraine, (2) episodic cluster headache, and (3) neither migraine nor cluster headache) and each of the comparator cohorts with respect to demographics, clinical characteristics, medication use, and rates of study outcomes as identified in administrative claims. Once the target sample size is reached, we will conduct comparative analyses for pregnancy, maternal and infant outcomes, comparing galcanezumab-exposed pregnancies with comparator pregnancies.

Population

Phase 1: For uptake monitoring, we will identify a cohort of women exposed to galcanezumab during pregnancy, defined as receiving at least 1 dispensing of galcanezumab within 5 half-lives (135 days) before LMP or any time during pregnancy. All inclusion and exclusion criteria planned for Phase 2 will be applied to ascertain the available sample size for descriptive and comparative analyses. Medication dispensings will be identified by pharmacy or medical claims in the HIRD. The galcanezumab cohort will be stratified into subcohorts based on whether the patient had (1) migraine, (2) episodic cluster headache, or (3) neither migraine nor cluster headache prior to the end 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 groups have been considered. Primary analyses will focus on the active comparator group comprising women using non-CGRP-antagonist migraine prophylaxis medications during pregnancy. We will conduct comparative analyses when patient accrual reaches the target size for the galcanezumab exposed cohort, noting that additional databases will be identified and added to the study should uptake monitoring show that accrual of a sufficient sample size in the HIRD alone is infeasible within the planned timeline. Comparator cohorts will include the following:

- Women with migraine with exposure to oral migraine prophylaxis medications within 5 half-lives prior to LMP or any time during pregnancy (primary analyses):
    - Pregnant women with migraine (defined throughout as at least 1 diagnosis of migraine or dispensing of a triptan during or at any time prior to LMP among women with no diagnosis of cluster headache during the same interval) who are treated with at least 1 medication used for migraine prophylaxis (amitriptyline, nortriptyline venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, or nadolol) within the period beginning 5 half-lives prior to LMP 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 (eg, valproate and divalproex will be included in analysis of pre-eclampsia but excluded from analyses of major congenital malformations, see Annex 1).
- Women with migraine who were not exposed to any migraine prophylaxis medications within 5 half-lives prior to LMP or any time during pregnancy (secondary analyses), which will include the following 3 comparator groups:
    - Pregnant women with a migraine diagnosis or treatment with triptans any time before or during pregnancy.
    - Pregnant women who are treated with triptans within 5 half-lives before LMP or any time during pregnancy.
    - Pregnant women with a migraine diagnosis and prior history of non-oral CGRP-antagonist use, who were not exposed to a CGRP-antagonist during 5 half-lives prior to LMP or any time during pregnancy
- Pregnant women without migraine diagnosis, a cluster headache diagnosis, triptan use, or exposure to galcanezumab or other CGRP-antagonist medications any time before or during pregnancy.

Variables

In Phase 1, uptake monitoring, exposure to galcanezumab will be ascertained from claims for outpatient pharmacy dispensings, as well as injections administered in a health care setting.

In Phase 2 descriptive analyses, exposure to galcanezumab and other migraine prophylaxis medications will be ascertained from claims for outpatient pharmacy dispensings, as well as injections 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. For comparative analyses, information from claims on exposures, outcomes and covariates, including demographics, clinical characteristics, healthcare utilization, and medication use, will be augmented using medical record data. We will request medical record data to confirm study outcomes and the timing of the start of pregnancies to be included in the primary analysis (eg, all pregnant women exposed to galcanezumab or comparator migraine prophylactic medications during pregnancy), and a random sample of pregnancies from secondary comparator cohorts. Validation of outcome

algorithms applied to the claims will be performed using medical record data as a gold standard. Covariates only partially ascertained in administrative claims, such as lifestyle factors (eg, smoking status, BMI, 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 BMI, smoking, and alcohol use.

If the 2024 uptake monitoring report suggests that an adequate sample size to meet both primary objectives cannot be attained in the HIRD by the end of the uptake monitoring phase (2026), additional databases will be identified so that so that planned study size is achieved and comparative analyses can be executed with adequate statistical power.

Study size

Infant/Fetal Outcomes:

The primary fetal/infant outcome of interest is major congenital malformations. 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 (Centers for Disease Control and Prevention 2008), 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 linked pairs and approximately 1800 unexposed linked pairs.

Maternal Outcomes:

The primary maternal outcome of interest is the risk for pre-eclampsia. Assuming that pre-eclampsia occurs in approximately 3% of pregnancies in the general population (Anath et al. 2013), 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 will be identified, and planned study entry criteria for Phase 2 will be applied to ascertain available cohort size. Patients in the galcanezumab cohort will further be categorized into sub-cohorts defined by (1) migraine, (2) episodic cluster headache, or (3) neither migraine nor cluster headache.

In Phase 2 descriptive analyses, the number of women of child-bearing age, pregnant women, and mother-infant pairs who are exposed to galcanezumab and all comparator groups will be identified. Patients in the galcanezumab cohort will further be categorized into cohorts and sub-cohorts defined by (1) migraine, (2) episodic cluster headache, or (3) neither migraine nor cluster headache. We will describe distributions of covariates including demographics, comorbidity, medications, and health care utilization overall, and separately by cohort/sub-cohort. The proportion of pregnancies affected or birth prevalences (as applicable), along with the 95% 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 (1) migraine, (2) episodic cluster headache, or (3) neither migraine nor cluster headache among the galcanezumab exposed cohort.

Once the target sample size has been reached, 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 five comparator cohorts.

Propensity scores will be used to balance baseline covariates to control confounding between the galcanezumab cohort and the 5 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, sufficient size to support comparative analyses within the cluster headache cohort is not expected to be achieved, and comparative analyses in this subcohort will not be conducted and only descriptive analysis will be performed. Except for instances where <11 exposed mothers or mother-infant pairs (as applicable) are observed in a given stratum (as privacy rules require masking of cell sizes <11), effect estimates will be stratified by 5 exposure windows: 5 half-lives before LMP, during each trimester and throughout the pregnancy. We do expect that stratified analyses will not meet sample size requirements for 80% power. Given that we may only be able to acquire approximately 40% of requested medical records with variation by disease state and population of interest within the HIRD (HealthCore, internal communication), and incomplete capture by medical records of certain lifestyle risk factors, we will address missing covariate data using multiple imputation. Further, validation of algorithms to identify study outcomes will yield algorithm performance characteristics that can be used to inform quantitative bias analysis to formally assess the impact of outcome misclassification.

Sensitivity analyses 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 LMP (as sample size allows). Other sensitivity analyses include extension of baseline covariate ascertainment for

chronic conditions to 90 days after the estimated start of the LMP so that preexisting conditions documented at the first prenatal visit are captured, capturing galcanezumab and comparator medication dispensings that occurred only during pregnancy, stratification by timing of exposure prior to LMP, and an extended prepregnancy washout period of 90 days, removal of the health plan enrollment requirements and infant linkage for outcomes where these are required, and consideration of subgroups based on maternal age at delivery. As results are masked for privacy purposes if counts in an individual stratum are <11, subgroup analyses will not be performed only where <11 exposed mothers or mother-infant pairs (as applicable) are observed in a given stratum, noting that power may be insufficient in these subgroup analyses where sample size is low.

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 study population. Records will be submitted to clinical experts for adjudication for primary outcomes and any secondary outcomes that present a potential safety signal (eg, an estimated risk ratio of above 2.0 or a statistically significant effect) in primary analyses.

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 based on regulated timelines. An 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, which will coincide with the final study report requirement for EMA, and will include descriptive analyses only unless the target sample size has been reached. A final report of study results including both descriptive and comparative analysis will be provided to the FDA by 31 December 2027.

5. Amendments and Updates

Amendment or update number	Date	Section of study protocol	Amendment or update	Reason
1	19 June 2020	8	Objectives have been revised to indicate that comparative analyses of major congenital malformation and pre-eclampsia risk are primary objectives. An additional comparator group (migraine patients without prophylaxis) and two additional secondary outcomes (low birthweight and eclampsia) have been added.	Modification required by the Food and Drug Administration (FDA)
1	19 June 2020	9.1	New figures have been added for clarity. Phase 1 has been modified to include only uptake monitoring. Phase 2, now including both descriptive and comparative analyses, will now be pursued regardless of whether adequate sample size is observed in the HealthCore Integrated Research Database (HIRD).	Modification required by the FDA
1	19 June 2020	9.2	Clarifying edits have been implemented throughout. New exclusion criteria based on history of epilepsy and severe cardiovascular disease have been added.	Concerns have been raised about potential confounding by indication in patients with comorbid indications for migraine prophylaxis.
1	19 June 2020	9.2.2	The acceptable age range has been modified to 15-49 years, an additional comparator group (migraine patients without prophylaxis) has been added, and exposure timing has been revised to rely on five half-lives prior to the estimated start of the last menstrual period. Clarification on subgroups excluded in assessment of malformation outcomes has been added.	Modification required by the FDA

Amendment or update number	Date	Section of study protocol	Amendment or update	Reason
1	19 June 2020	9.2.3	Timing of analyses has been clarified, and tentative language concerning execution of comparative analyses only if adequate power is reached in the HIRD has been removed. Additional operational details, including code appendices, have been added to the protocol rather than placed in the statistical analysis plan (SAP) alone.	Modification required by the FDA
1	19 June 2020	9.3.1	Additional operational detail on exposures, including applicable codes and considerations related to combination product use, has been added in a supporting appendix and throughout the text. Exposure will be defined based on product half lives in the main analysis, and comment on expected etiologically relevant windows has been added.	Modification required by the FDA
1	19 June 2020	9.3.2	Additional detail, including clinical definitions and linked appendices for screening codes, has been added to discussion of study outcomes. Low birthweight and eclampsia have been added as new secondary outcomes.	Modification required by the FDA
1	19 June 2020	9.3.3	The planned list of covariates has been substantially expanded to include new demographic and clinical characteristics, conditions and medications that will result in exclusion from analysis of malformations, vaccines during pregnancy, and other characteristics of interest. Operational details and administrative codes have been added as a supporting appendix.	Modification required by the FDA

Amendment or update number	Date	Section of study protocol	Amendment or update	Reason
1	19 June 2020	9.4	Study size discussion has been expanded to consider database size, possible obstacles to attaining the target sample size, and considerations in support of limiting comparative analyses to migraine patients.	Modification required by the FDA
1	19 June 2020	9.6	Clarifying edits have been made to increase transparency. New sensitivity analyses varying the exposure window and considering maternal age strata have been added.	Modification required by the FDA
1	19 June 2020	Annex 3	An extensive listing of planned codes and other operational details in support of the protocol has been added.	Modification required by the FDA
2	02 October 2020	9.4	Additional details have been added to the study size section in order to (1) facilitate reproduction of sample size estimates, and (2) project expected accrual of galcanezumab-exposed pregnancies through 2026.	Modification required by the FDA
3	See date on front page	Annex 3	Amended to remove the code list (Annex 3), making it a standalone document, referenced in Annex 1.	This change will allow for more frequent QC and updates to code lists as the study is implemented.
3	See date on front page	9.3.3; Annex 3	Removal of aminopterin and diethylsilbesterol from the teratogenic medication list .	These drugs are no longer on the market and no NDC codes exist.

6. Milestones

Milestone	Planned date
Start of data collection (European Medicines Agency [EMA]/Food and Drug Administration [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 periodic safety update reports starting 30 November 2019
EMA Interim report	31 December 2022
FDA Interim report	31 December 2024
Registration in the European Union Post-authorisation studies 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 4 to 72 hours and usually accompanied by other symptoms including nausea, vomiting, sensitivity to light and sound, and changes in vision (Katsarava et al. 2012). 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 or more 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 (Lipton et al. 2007; Buse et al. 2012).

Cluster headache is one of the most severe primary headache syndromes and is characterized by recurrent attacks of intense headaches on 1 side of the head, frequently associated with pain behind or around 1 eye, restlessness and agitation (Ashkenazi et al. 2011). A cluster period generally lasts from 6 to 12 weeks and a single attack typically lasts between 15 minutes and 3 hours (Headache Classification Committee of the International Headache Society [HIS] 2013). Cluster headache has been associated with seasonal changes with higher incidence of attacks reported in the fall and spring (Costa et al. 2015). The International Headache Society classified cluster headache into 2 major temporal types: episodic (85% to 90%) and chronic (10% to 15%). The prevalence of overall cluster headache is approximately 0.1% and it mostly affects men with overall male-to-female ratio of 4 to 1 (Fischera et al. 2008).

Galcanezumab is a humanized monoclonal antibody that selectively binds to CGRP and inhibits its activity. Elevated blood concentrations of CGRP have been associated with migraine or cluster headache attacks (Durham 2008). 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) (Forderreuther et al. 2018). 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 to 3 comparing galcanezumab with placebo; results were presented at the 2018 American Headache Society annual meeting (Goadsby et al. 2019). Emgality™ (galcanezumab), a once-monthly, subcutaneous 120-mg injection, which has a half-life of 27 days, has received approval from the 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 4 migraine days per month, on 14 November 2018. Emgality™ (galcanezumab), 300 mg subcutaneously once monthly, was also approved in the US for the treatment of episodic cluster headache on 04 June 2019.

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 (Buse et al. 2012) 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 (Cassina et al. 2010). It is anticipated that given the treated patient population and the long half-life of galcanezumab, exposure during pregnancy will occur in the postauthorization 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 (Banhidy et al. 2007; Facchinetti et al. 2009). In the migraine population, more severe migraine is associated with increased prevalence of CV comorbidity, as well as anxiety and depression (Chen et al. 2012). 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 postauthorization 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 objective of this study is to compare the risk of (1) major congenital malformations, and (2) pre-eclampsia, among women with migraine who are treated with galcanezumab during pregnancy and women included in the following comparator groups:

- Primary comparator group:
    - Women with migraine treated with oral non-CGRP-antagonist medications for migraine prophylaxis within 5 half-lives before LMP or any time during pregnancy with no use of CGRP-antagonist medications within 5 half-lives before LMP or any time during pregnancy.
- Secondary comparator groups:
    - Women with migraine who were not exposed to migraine prophylaxis within five half-lives before the LMP or any time during pregnancy, separately for:
        - Pregnant women with a migraine diagnosis or treatment with triptans any time before or during pregnancy.
        - Pregnant women who are treated with triptans within 5 half-lives before LMP or any time during pregnancy.
        - Pregnant women with a migraine diagnosis and prior history of non-oral CGRP-antagonist use, who were not dispensed a CGRP-antagonist at least 5 half-lives prior to LMP.
    - Women without a migraine diagnosis, a cluster headache diagnosis, triptan use, or exposure to galcanezumab or other CGRP-antagonist medications any time before or during pregnancy.

Secondary objectives are to:

- Monitor exposure to galcanezumab during pregnancy in women with (1) migraine, (2) episodic cluster headache, and (3) neither migraine nor cluster headache to inform subsequent timing and feasibility of comparative analysis.
- Conduct comparative safety analyses of maternal, pregnancy and fetal/infant outcomes between pregnant women with migraine exposed to galcanezumab with each of the aforementioned comparator groups. Secondary pregnancy, maternal, and fetal/infant outcomes of interest include:
    - Pregnancy outcomes: recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery.
    - Maternal outcomes: hypertension during pregnancy and eclampsia.
    - Fetal/infant outcomes: small for gestational age, low birthweight, and minor congenital malformations.

- Describe patient characteristics and occurrence of pregnancy, maternal, and infant outcomes among women in the galcanezumab (separately for women with (1) migraine, (2) episodic cluster headache, and (3) neither migraine nor cluster headache) and comparator cohorts.

9. Research Methods

9.1. Study Design

This is a cohort study using secondary data will include two phases. A summary of the study plan is shown in Figure 1.

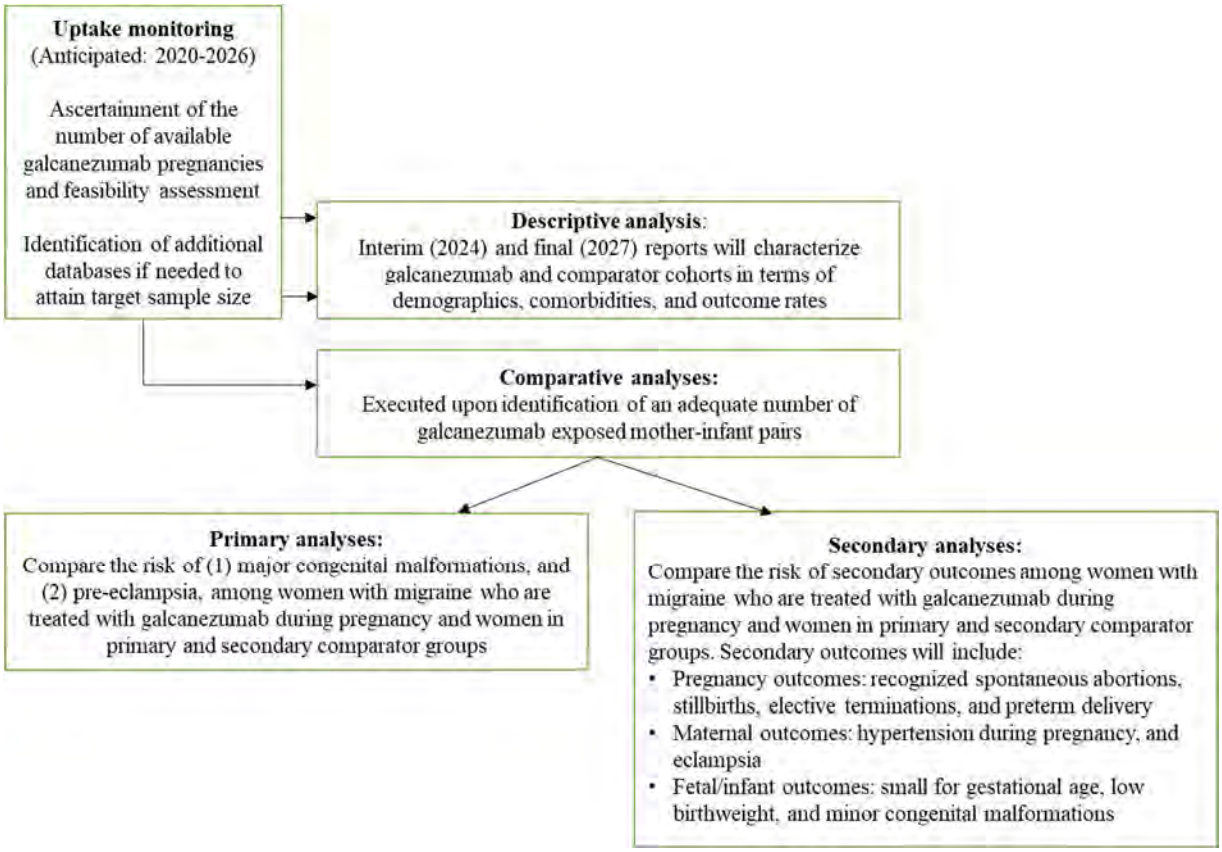


Figure 1. Study design overview.

Phase 1: Galcanezumab uptake monitoring

The purpose of study Phase 1 is to monitor the total number of pregnant women exposed to galcanezumab during or within 5 half-lives (135 days) prior to LMP (see Section 9.2.2, Study Population). Patient counts showing attrition based on each inclusion and exclusion criterion, linkage between mothers and infants, and high-level descriptive analyses will be shown overall and among sub-cohorts defined by (1) migraine (defined throughout as diagnosis of migraine or dispensing of a triptan among patients with no diagnosis of cluster headache), (2) episodic cluster headache (defined throughout as at least 1 diagnosis of episodic or unspecified cluster headache with no diagnosis of chronic cluster headache), or (3) neither migraine nor cluster headache (See Section 9.2.2.1, Phase 1 Uptake Monitoring).

Uptake monitoring will occur annually for 2020 through 2026. After each monitoring cycle, overall patient accrual will be compared against the target sample sizes (ie, 430 galcanezumab

exposed mother-infant pairs meeting all study entry criteria) to detect at least a 2-fold difference in the risks of pre-eclampsia for and major congenital malformations with at least 80% power to determine feasibility for Phase 2. If by the 2024 interim report extrapolation from product uptake through 2024 indicates that study size in 2026 will be below target, we will initiate a feasibility assessment to identify additional data sources for inclusion in the study. It is estimated that feasibility assessment can be completed and additional data sources enrolled within 2 years enabling study to adhere to timelines for completion of Phase 2 comparative analyses by the final study report in December of 2027.

Phase 2: Descriptive analysis

Patient characteristics including demographics, comorbidities, concomitant medication use, and health care utilization will be described. Cohorts will include pregnant women (1) exposed to galcanezumab, (2) exposed to migraine prophylaxis medications, (3) with migraine but not exposed to migraine prophylaxis medications (inclusive of (a) all unexposed women with migraine, (b) unexposed women with triptan use during pregnancy, and (c) women with past non-oral CGRP-antagonist use), and (4) without migraine. Additionally, only among the galcanezumab exposed cohort, these results will be stratified and reported and among cohorts/sub-cohorts defined by (1) migraine, (2) episodic cluster headache, or (3) neither migraine nor cluster headache (See Section 9.2.2.1, Phase 1 Uptake Monitoring).

Birth prevalence or proportion of pregnancies affected (as applicable) will be assessed for primary (major congenital malformations, pre-eclampsia) and secondary (recognized eclampsia, pregnancy hypertension, spontaneous abortions, stillbirths, elective terminations, preterm delivery, small for gestational age, low birthweight, and minor congenital anomalies) outcomes in all cohorts. Additionally, only among the galcanezumab exposed cohorts, these results will be stratified and reported and among cohorts/sub-cohorts defined by (1) migraine, (2) episodic cluster headache, or (3) neither migraine nor cluster headache (See Section 9.2.2.1, Phase 1 Uptake Monitoring).

Interim and final reports containing the results of these descriptive analyses based on administrative claims data will be developed during and at the end of galcanezumab uptake monitoring, prior to initiation of comparative analyses. An Interim Report to EMA will be completed in Q4 2022, and an Interim Report to FDA will be completed in Q4 2024.

Phase 2: Comparative analyses

When the target sample size (see Section 9.4, Study Size) is reached, we will conduct comparative analyses for all primary and secondary study outcomes, comparing women diagnosed with migraine with galcanezumab exposure from 5 half-lives prior to LMP through delivery with pregnant patients with women in the primary and secondary comparator groups (See Section 9.2.2.2, Phase 2 Comparative and Descriptive Analyses).

Administrative data will be supplemented with medical records review to verify the timing of pregnancy, outcomes and available covariates not captured in claims for galcanezumab users, the primary comparator group, and a sample of women from the other comparator groups.

Validation of algorithms used to identify outcomes in the claims data will use this medical record data as a gold standard and performance characteristics will be used to inform bias analysis. Medical record confirmation may be required for additional outcomes if the claims-based analysis shows a potential signal for increased risk (eg, a statistically significant effect or a risk ratio greater than 2.0 for outcomes where more than 10 events are observed within the comparison). 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 prevalence or birth prevalence rates and prevalence or birth prevalence ratios with applicable 95% 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. Medical records will be utilized to confirm endpoints and covariates that are thought to be incompletely captured in claims (eg, BMI, smoking, alcohol use) for the galcanezumab exposed and active comparator cohorts. Records will also be requested for a sample of patients from the secondary comparator cohorts.

9.2.1. Data Sources

Initial uptake monitoring will occur in the HIRD, a large administrative healthcare database maintained by HealthCore for use in health outcomes and pharmacoepidemiologic research. The HIRD is a longitudinal medical and pharmacy claims database from commercially-insured health plan members across the US. Member enrollment, medical care (professional and facility claims), outpatient prescription drug dispensings, outpatient laboratory test results, 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 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% to 75% of completed pregnancies could be connected to a qualifying infant. In cases where an 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.

If uptake monitoring suggests that adequate power is not expected by the projected end of Phase 1 (see Section 9.4, Study Size), additional study databases similar to the HIRD will be identified to increase the number of pregnancies needed for analysis.

9.2.2. Study Population

9.2.2.1. Phase 1: Uptake Monitoring

The **Galcanezumab Cohort** will include pregnant women meeting all of the following inclusion and exclusion criteria (Figure 1):

Inclusion criteria:

- Female sex.
- Age 15 to 49 years at the estimated first day of the LMP, see Section 9.2.3, Study Period).
- At least 1 pregnancy code.
- At least 1 pharmacy dispensing or injection in a health care setting for galcanezumab at any time from 5 half-lives (135 days) prior to the estimated LMP to until the end of pregnancy (Section 9.2.3, Study Period).
- Continuous medical and pharmacy coverage for at least 183 days prior to and including the estimated LMP.

Exclusion criteria:

- Insufficient data to define LMP (eg, diagnosis or procedure indicating pregnancy where health plan eligibility or the study period end before a pregnancy outcome can be observed, see Section 9.2.3, Study Period) using administrative claims data.
- Exposed to other CGRP-antagonist medications (see I5Q-MC-B003 Study Code Lists referenced in Annex 1) from 5 half-lives prior to the estimated LMP through delivery, because these medications may share class effects with galcanezumab.
- At least 1 diagnosis of epilepsy prior to the estimated LMP.
- At least 1 diagnosis of severe CV disease (CV malformation, myocardial infarction, hospitalization with CV events as the principal discharge diagnosis, or pulmonary hypertension) prior to the estimated LMP.
- At least 1 pharmacy dispensing for medications included in the primary comparator group (amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, nadolol, or timolol) from 5 drug-specific half-lives prior to the estimated LMP and until the end of pregnancy.
- At least 1 diagnosis of chronic cluster headache any time prior to or during pregnancy (noting that unspecified cluster headache will be assumed episodic and included).

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 5-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**, 3 additional cohorts meeting all the following criteria will be created as follows:

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

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.

9.2.2.2. Phase 2: Comparative and Descriptive 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 channeling 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):

- Primary comparator group: Women with migraine exposed to a non-CGRP-antagonist migraine prophylaxis medication during pregnancy:

- Pregnant women exposed during pregnancy to 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. The migraine prophylaxis cohort represents a variety of treatment modalities that may be used to manage severe migraine patients during pregnancy (Takaki et al. 2017) (excepting CGRP-antagonist 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:
        - Pregnancy outcomes (recognized spontaneous abortions, stillbirths, elective terminations, and preterm delivery): all medications will be used
        - Maternal outcomes (pre-eclampsia, hypertension during pregnancy, and eclampsia): divalproex, topiramate, and valproate will be used
        - Fetal/infant outcomes (major congenital malformations, small for gestational age, low birth weight and minor congenital malformations): amitriptyline, nortriptyline, and venlafaxine will be used

- Women diagnosed with migraine who were not exposed to migraine prophylaxis during pregnancy:
    - Pregnant women with migraine not treated with migraine prophylaxis during pregnancy
        - This cohort ensures that women have migraine by requiring either a diagnosis of migraine 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 (Marchenko et al. 2015; Spielmann et al. 2018). 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 (Lind et al. 2017).
            - For analyses of pre-eclampsia and hypertension, there is some evidence that disease severity may increase risk. Galcanezumab users may have more severe migraine than patients who do not require continued prophylaxis, which could increase the risk of these outcomes independently of medication use.

- Pregnant women with migraine treated with triptans (Triptan cohort)
    - This cohort ensures that women have migraine by requiring 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 (Marchenko et al. 2015; Spielmann et al. 2018). 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 (Lind et al. 2017).
    - Analyses of pre-eclampsia and hypertension may be biased in a less predictable direction. Triptans are contraindicated in patients with underlying uncontrolled hypertension, angina, and ischemic heart disease (Alwhaibi et al. 2016). As a result, patients prescribed triptans might also appear to have a lower risk for adverse CV 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.
- Pregnant women with migraine and prior history of non-oral CGRP-antagonist use, who discontinued therapy 5 half-lives or more prior to the estimated LMP (past CGRP cohort).
    - This cohort ensures that women are indicated for treatment with CGRP-antagonists 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.

- Pregnant women who do not have any diagnoses of migraine, use of triptans, or exposure to galcanezumab.
    - This cohort excludes women who are in the target population for galcanezumab and provides background incidence rates that (within the confines of propensity score adjusted analyses) are somewhat representative of the general population of the HIRD. Because women with migraine are excluded from the comparator cohort, migraine and its treatment are intractably confounded in this comparison and it will not be possible to determine whether any observed associations reflect effects of galcanezumab or migraine.

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

Inclusion criteria:

- Female sex.
- Age 15 to 49 years.

- At least 1 pregnancy within the study period (Section 9.2.3, Study Period)

For infant outcomes, mother-infant pairs will further be limited to those where the infant date of birth is 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 LMP (see Section 9.2.3, Study Period);
- Less than 6 months of continuous health plan eligibility available prior to the estimated LMP.
- Exposure to CGRP-antagonist medications other than galcanezumab from 5 half-lives prior to the estimated LMP through delivery, noting that these medications may share class effects with galcanezumab.
- At least 1 diagnosis of epilepsy prior to the estimated LMP.
- At least 1 diagnosis of severe CV disease (CV malformation, myocardial infarction, hospitalization with CV events as the principal discharge diagnosis, or pulmonary hypertension) prior to the estimated LMP.
- At least 1 diagnosis of cluster headache prior to and until the end of pregnancy.

For analyses of malformations, mother-infant pairs with exposure to known severely teratogenic medications within 6 months before LMP or during pregnancy, infections known to cause birth defects during pregnancy, diagnosis of alcohol dependence, or recognized chromosomal anomalies will be excluded. A full list of these medications and diagnoses is shown in I5Q-MC-B003 Study Code Lists referenced in Annex 1.

Additional cohort-specific considerations

Galcanezumab exposed cohort:

- Inclusion:
  - At least 1 diagnosis of migraine or dispensing of triptans at any time during or prior to pregnancy.
  - At least 1 dispensing or administration of galcanezumab, within 5 half-lives before the estimated LMP or any time during pregnancy (Section 9.2.3, Study Period).
- Exclusion:
  - At least 1 pharmacy dispensing for medications included in the primary comparator group (amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, nadolol, or timolol) from 5 drug-specific half-lives prior to and until the end of pregnancy.

Composite migraine prophylaxis exposed cohort:

- Inclusion:
  - At least 1 diagnosis of migraine or dispensing of triptans at any time during or prior to pregnancy.
  - At least 1 dispensing of at least 1 of the following migraine prophylaxis medications: amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, or nadolol within 5 half-lives before LMP or any time during pregnancy (see I5Q-MC-B003 Study Code Lists referenced in Annex 1) of the estimated LMP (Section 9.2.3, Study Period).
- Exclusion:
  - Exposure to galcanezumab from 5 half-lives prior to the estimated LMP through delivery.

Women diagnosed with migraine who were not exposed to migraine prophylaxis during pregnancy cohort:

- Inclusion:
  - At least 1 diagnosis of migraine or dispensing of triptans at any time during or prior to pregnancy.
- Exclusion:
  - Exposure to galcanezumab from 5 half-lives prior to the estimated LMP through delivery.
  - At least 1 dispensing of at least 1 of the following migraine prophylaxis medications: amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, or nadolol within 5 half-lives before the estimated LMP or any time during pregnancy (See Annex 1) of the estimated LMP (Section 9.2.3, Study Period).

Triptan cohort:

- Inclusion:
  - A qualified exposed pregnancy must have at least one dispensing of triptans within five half-lives before the LMP or any time during pregnancy (Section 9.2.3, Study Period).
- Exclusion:
  - Exposure to galcanezumab from five half-lives prior to LMP through delivery.
  - 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 from five half-lives prior to the estimated LMP through delivery (see I5Q-MC-B003 Study Code Lists referenced in Annex 1; Section 9.2.3, Study Period).

- Note: When comparing the galcanezumab and triptan cohorts, galcanezumab users with triptan exposure from 5 half-lives prior to LMP through delivery will be excluded.

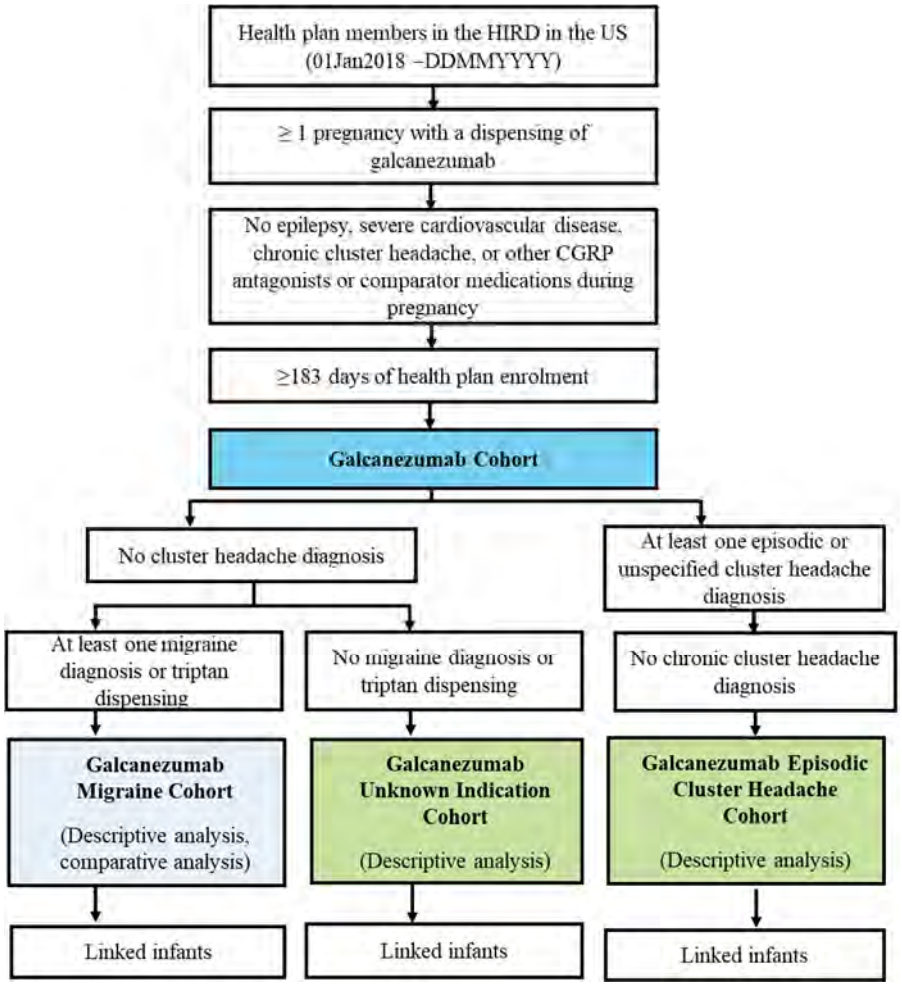
Past CGRP Cohort:

- Inclusion:
  - A qualified pregnancy must have past exposure to CGRP-antagonists discontinued at least 5 half-lives prior to the estimated LMP and no exposure to prophylactic migraine medications (including galcanezumab) from 5 half-lives prior to the estimated LMP through delivery.
- Exclusion:
  - Exposure to galcanezumab from 5 half-lives prior to the estimated LMP through delivery.
  - At least 1 dispensing of at least 1 of the following migraine prophylaxis medications: amitriptyline, nortriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, timolol, or nadolol from 5 half-lives prior to the estimated LMP through delivery (see I5Q-MC-B003 Study Code Lists referenced in Annex 1; Section 9.2.3, Study Period).

Non-migraine cohort:

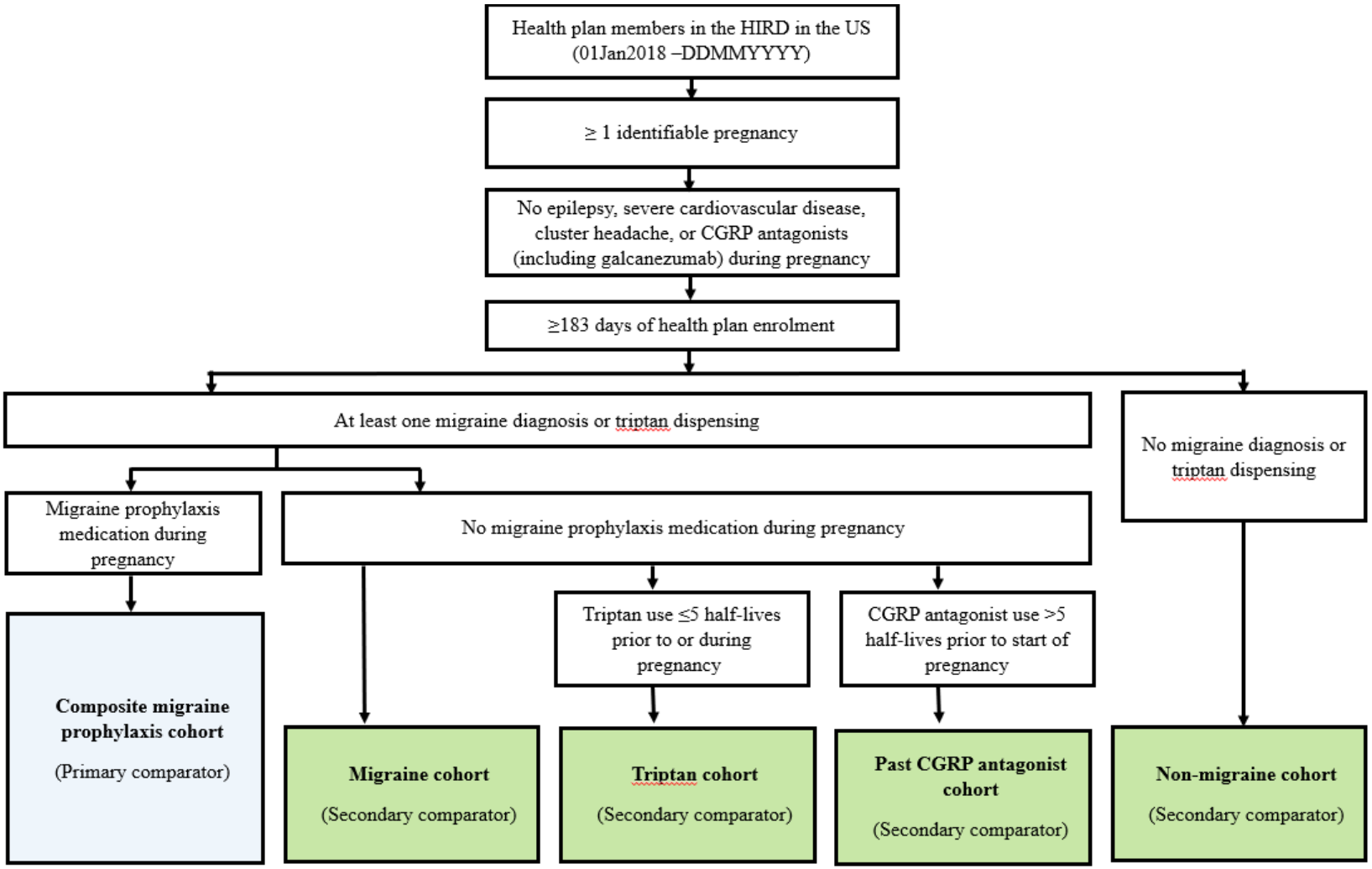
- Exclusion:
  - Exposure to galcanezumab or CGRP antagonists at any time prior to or during pregnancy.
  - At least 1 diagnosis of migraine or one dispensing or triptans at any time prior to or during pregnancy.

For the Phase 2 cohorts, all patients meeting these criteria will be included in the analyses.



Abbreviations: CGRP = calcitonin gene-related peptide; HIRD = HealthCore Integrated Research Database.

Figure 2. Flow diagram showing the composition of the study population for Phase 1 (uptake monitoring).



Abbreviations: CGRP = calcitonin gene-related peptide; HIRD = HealthCore Integrated Research Database.

Figure 3. Diagram showing the composition of the comparator study populations for Phase 2.

9.2.3. Study Period

9.2.3.1. Timing of Analyses

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 EMA on 31 December 2024 and 30 June 2026 for final submission to the FDA on 31 December 2027.

Phase 2

Descriptive analyses will be described in 2 interim reports during uptake monitoring. The first Interim Report to EMA will be completed in Q4 2022, and the second Interim Report to FDA will be completed in Q4 2024. Final reports containing descriptive analyses for all cohorts will be completed prior to the start of comparative analyses.

The comparative analyses for Phase 2 will be initiated once the target number of galcanezumab exposed mother/infant pairs are accrued, noting that additional data beyond the HIRD may be obtained if needed as ascertained via uptake monitoring.

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.

9.2.3.2. Pregnancy Ascertainment

Pregnancies will be identified using the administrative Current Procedural Terminology, HCPCS, and ICD-10 codes shown in I5Q-MC-B003 Study Code Lists referenced in Annex 1. A patient with at least 1 code relating to prenatal care, termination, or delivery will be counted as a pregnancy and tabulated. However, only pregnancies with an identifiable beginning and end will be included in the analyses. Because administrative claims data do not specifically identify the date of the LMP, we will identify LMP using a 2-phased approach. In the first phase, the following broad criteria will be used to assign LMP in claims-based screening:

- Where a gestational age-specific code is recorded at infant delivery or pregnancy termination, we will subtract the specified number of weeks from the delivery date to establish an estimated LMP. Given that these codes have been required for reimbursement since late 2018, they are expected to be commonly used.

- Where a gestational age code is not recorded at the end of pregnancy, but a gestational age-specific code is recorded during prenatal care, the last gestational age code recorded prior to delivery will be used to establish the LMP.
- 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 and no diagnosis codes suggesting preterm delivery, we will consider the LMP to have occurred 42 weeks prior to the date of delivery.
    - For women with documentation of a preterm delivery without a specified gestational age, we will consider the LMP to have occurred 36 weeks prior to the date of delivery.
    - For women with no documentation of gestational age with procedure codes indicative of care received at a typical gestational age, we will infer gestational age (HealthCore internal algorithm).
    - For women with documentation of a spontaneous or elective termination, we will consider the LMP to have occurred 20 weeks prior to the date of the pregnancy outcome.

A similar approach to identify the estimated LMP has been applied in past studies for full-term and preterm deliveries (Cole et al. 2007; Katsarava et al. 2012; Mines et al. 2014;). 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 (CDC resources page [WWW].

Where the end of pregnancy falls outside of the dates when HIRD data are available and/or the patient's continuous health plan eligibility, the pregnancy window cannot be defined without use of strong assumptions and outcomes cannot be ascertained. Instances where the outcome of a pregnancy is not documented (eg, a prenatal care claim is followed by no further documentation of pregnancy, termination, or delivery where the patient remains enrolled in the health plan) may also be observed. The number of these possibly exposed pregnancies will be tabulated for when showing formation of the study cohorts. However, they will not be included in the descriptive or comparative analyses. We may reassess this approach to determine if there are opportunities to retain patients with partial capture of pregnancy in time-varying analyses in the comparative analysis phase; intention to make this change will be documented in interim and/or final descriptive reporting prior to execution of comparative analyses.

For women with study medication exposure during pregnancy or prior to the LMP, the study period will be divided into the prepregnancy baseline period (minimum duration of 6 months), the pregnancy period (overall and by trimester), and the 6-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), outcome ascertainment 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 4.

- Patient A is followed from the start of her continuous health plan eligibility through her full-term pregnancy and 6 weeks postpartum. Her linked infant is then followed until age 1 year.
- Patient B is followed from the start of her continuous health plan eligibility through her preterm 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 6-week postpartum 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.

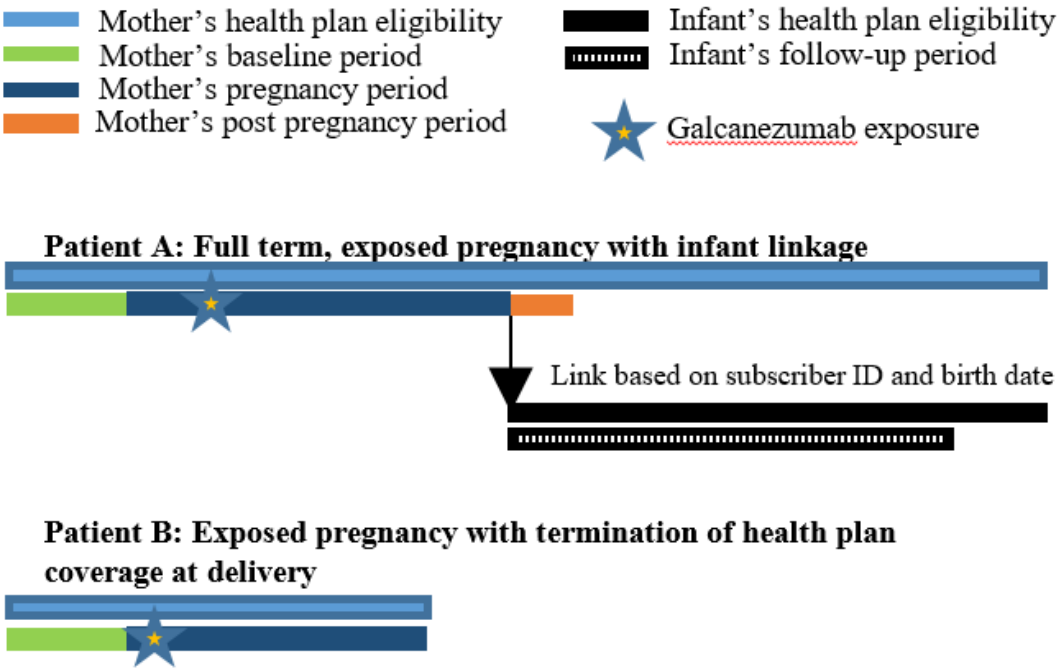


Figure 4. Observation periods.

9.3. Variables

9.3.1. Exposures

Exposure to galcanezumab or comparator medications (eg, triptans or composite migraine prophylaxis medications) will be ascertained based on outpatient pharmacy dispensings and injections that occur in a health care setting. Specific applicable codes are shown in I5Q-MC-B003 Study Code Lists referenced in Annex 1. We will define an exposure to galcanezumab as a dispensing or administration of a study drug that occurs during the 5 half-lives prior to the estimated LMP 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 5 half-life prepregnancy interval has been specified to account for the long elimination half-life of galcanezumab (27 days).

For women in the composite migraine prophylaxis group, exposure will be defined as a dispensing during pregnancy or a prepregnancy exposure window prior to pregnancy of 5 half-lives of the applicable medication (see I5Q-MC-B003 Study Code Lists referenced in Annex 1). Timing of exposure will be varied in sensitivity analyses (see Section 9.6.3, Sensitivity Analyses) The etiologically relevant window is expected to vary by study outcome, and as such, the exposure window of interest will vary as defined in the Phase 2 SAP. For all outcomes, the main exposure of interest will be described in addition to exposure prior to but not during pregnancy and during each trimester.

For women in the comparator group with prior exposure to CGRP-antagonists, evidence of discontinuation of migraine prophylaxis medications will be ascertained by evidence of dispensings followed by the absence of any dispensings for 5 half-lives 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 interim descriptive analyses, administrative claims data will be used to identify each outcome on the basis of ICD-10 diagnosis and procedure, Current Procedural Terminology, and HCPCS codes as shown in I5Q-MC-B003 Study Code Lists referenced in Annex 1. In support of comparative analyses, medical records will be sought for all women and infants in the galcanezumab and migraine prophylaxis exposed cohorts and for each claims-identified outcome of pre-eclampsia, and major congenital malformation, noting that any outcome not captured in the claims data that is identified during medical record review will be counted as a confirmed outcome. Given that few validation studies are available in ICD-10 and their results may not be transportable across populations and databases, performance of algorithms to identify these outcomes will be validated, and algorithms may be refined based on the results of internal validation via medical record review. Outcomes identified in claims where medical records are not available will be classified as unconfirmed outcomes.

Criteria to ascertain each individual malformation will follow definitions and groupings typically used by the MACDP, noting that MACDP codes are not directly available in the HIRD. For these challenging outcomes, 2 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 first from the mother's medical claims (see I5Q-MC-B003 Study Code Lists referenced in Annex 1 for relevant administrative codes). Clinical definitions include the following:

- Pre-eclampsia (primary outcome) clinically defined as new onset hypertension occurring after 20 weeks of gestation with new-onset proteinuria or without proteinuria but with any of the following severe features: thrombocytopenia (platelet count less than 100,000/µL); impaired liver function as indicated by abnormally elevated blood concentrations of liver enzymes (to twice the upper limit of normal concentration); severe persistent right upper quadrant or epigastric pain and not accounted for by alternative diagnoses; renal insufficiency (serum creatinine concentration greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease); pulmonary edema; or new-onset headache unresponsive to acetaminophen and not accounted for by alternative diagnoses or visual disturbances.
- Recognized spontaneous abortions: pregnancies where the patient sought medical care related to spontaneous termination of a pregnancy prior to 20 weeks gestational age.
- Stillbirth: fetal death prior to delivery in a pregnancy of at least 20 weeks gestational age.
- Elective termination: pharmacologic or surgical termination of a pregnancy by a healthcare provider prior to 20 weeks gestational age.
- Gestational hypertension: clinically defined as hypertension (blood pressure of 90 mm Hg or more, or both, on 2 occasions at least 4 hours apart) without proteinuria or severe features that develops after 20 weeks of gestation in a woman with a previously normal blood pressure and blood pressure levels return to normal in the postpartum period (Mammaro et al. 2009). Capture may be limited as the diagnosis is often applied retrospectively (CDC resources page [WWW]).
- Eclampsia: clinically defined as new-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use, in a woman with hypertensive disorder of pregnancy.

- Outcomes that will be identified from medical claims from either the mother or her linked infant within 1 month of the end of the pregnancy (which allows for capture of data not recorded at the initial hospitalization):
  - Preterm delivery; delivery less than 37 weeks gestational age.
  - Small for gestational age infants; birth weight below the 10th percentile for gestational age (inclusive of intrauterine growth restriction).
  - Low birth weight; birth weight <2,500 grams.

- 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 105th day of pregnancy and the end of the 6-week postpartum 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 I5Q-MC-B003 Study Code Lists referenced in Annex 1 noting that clinical definitions will utilize recommendations from the MACDP.
        - A composite of all major congenital malformations is a 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.
        - Outcomes that are associated with prematurity (eg, patent ductus arteriosus in an infant delivered prior to 37 weeks gestational age) or found by medical record review to indicate positional effects not identifiable in administrative claims (eg, positional plagiocephaly) will not be included.
        - Minor malformations will also be assessed both as a composite, by class, and within classes where defects are identified, by specific defect. Because minor congenital malformations typically pose few health consequences, we expect that their ascertainment in administrative claims may be poor.
        - For analysis of major and minor congenital malformations, we will exclude the following infants (see I5Q-MC-B003 Study Code Lists referenced in Annex 1 and Section 9.3.3, Covariates):
            - Syndromic or chromosomal cause (eg, 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 where the pregnancy was impacted by infections known to cause malformation.
            - Infants with prenatal exposure to known teratogens.

9.3.3. Covariates

In descriptive and comparative analyses, the variables listed below will be defined for mothers included in the cohort. Operational definitions and codes are shown in I5Q-MC-B003 Study Code Lists referenced in Annex 1. All variables will be identified during the prepregnancy baseline period unless otherwise specified.

- Demographic and general characteristics:
    - Age (years) at start of pregnancy

- Race/ethnicity as imputed on the basis of the American Community Survey (Davern et al. 2009)
- 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:
  - Comorbidities ascertained prior to the estimated LMP:
    - Anemia
    - Anxiety
    - Bipolar disorder
    - Chronic pulmonary disease
    - Dependence (alcohol and substance use)
    - Depression
    - Diabetes 1 and 2
    - Gout
    - Hyperlipidemia
    - Hypertension
    - Infertility
    - Malignancy
    - Obsessive compulsive disorder
    - Overweight and obesity, as available in claims
    - Panic disorder
    - Polycystic ovarian syndrome
    - Renal disease
    - Sleep disorders
    - Tobacco use, as available in claims
    - Thyroid disorders
    - Uterine anomalies
  - Comorbidities ascertained from the LMP through delivery:
    - Infections of teratogenic potential (noting that these patients are excluded from analysis of malformations):

- Toxoplasmosis
  - Syphilis
  - Varicella-Zoster
  - Parvovirus B19
  - Rubella
  - Cytomegalovirus
  - Herpes
  - Human immunodeficiency virus
  - Zika virus
- Cardiovascular diseases newly identified during pregnancy (noting that serious CV events prior to the LMP constitute an exclusion criterion)
  - Myocardial infarction
  - Transient ischemic attack
  - Ischemic stroke
  - Ischemic heart disease
  - Angina
  - Heart failure
  - Cardiac arrhythmia
  - Hemorrhagic stroke
  - Peripheral vascular disease
- Epilepsy diagnosed during pregnancy

o Headache diagnoses identified at any time prior to or during pregnancy:

- Migraine type (eg, with versus without aura), severity (with versus without intractable pain), and syndrome (eg, menstrual migraine, hemiplegic migraine, etc.)
- Cluster headache type (episodic versus unspecified) and severity (with versus without intractable pain)
- Other headache diagnoses:
  - Tension headache
  - Post-traumatic headache
  - Paroxysmal hemicrania
  - Trigeminal neuralgia

        - Occipital neuralgia
    - 25 most frequently occurring diagnoses recorded at the 3-digit level of the ICD-10 diagnosis code or Healthcare Cost and Utilization Project's Clinical Classifications Software (for descriptive analyses)
- Medication use (defined separately in the six months prior to and during pregnancy) will be identified based on Generic Product Identifier or HCPCS codes as applicable:
    - Use known or strongly suspected teratogens at any time during or within six months prior to LMP (Note: excludes the mother-infant pair from analysis of major and minor congenital anomalies. See I5Q-MC-B003 Study Code Lists referenced in Annex 1 for rationale behind inclusion of each medication):
        - angiotensin converting enzyme inhibitors
        - Acitretin
        - Aliskiren
        - Ambrisetan
        - Bosentan
        - Carbamazepine
        - Danazol
        - Griseofulvin
        - Isotretinoin
        - Lamotrigine
        - Leflunomide
        - Lenaliomide
        - Lithium
        - Macitentan
        - Methimazole
        - Methotrexate
        - Methylene blue
        - Misoprostol
        - Mycophenolate mofetil
        - Paramethadione
        - Penicillamine
        - Phenobarbital
        - Phenytoin, Fosphenytoin

- Pomalidomide
- Ribavirin
- Riociguat
- Thalidomide
- Topiramate
- Triazolam
- Trimethadione
- Valproate/valproic acid/divalproex
- Warfarin

- Use of medications with possible teratogenicity from six months prior to LMP through delivery:
  - Alprazolam
  - Aminoglycodsides
  - Amiodarone
  - Anastrozole
  - Angiotensin II receptor blockers
  - Aspirin
  - Atenolol
  - Bismuth subsalicylate
  - Clonazepam
  - Cortisone
  - Cyclophosphamide
  - Diazepam
  - Edoxaban
  - Fluconazole, Voriconazole
  - Flunisolide
  - HMG Co-A Reductase Inhibitors
  - Hydroxychloroquine
  - Hydroxyurea
  - Ibuprofen
  - Meloxicam

- Midazolam
- Ondansetron
- Potassium iodide
- Primaquine
- Propylthiouracil
- Tamoxifen
- Tetracycline antibiotics
- Trimethoprim-sulfamethoxazole
- Zoledronic acid

- Vaccines received from 6 months prior to LMP through delivery:
  - Influenza
  - Tetanus, diptheria, and acellular pertussis
  - Hepatitis A
  - Hepatitis B
  - Human papillomavirus
  - Measles, mumps and rubella
  - Meningococcal
  - Pneumococcal
  - Varicella
- Other medication use:
  - Anticoagulants
  - Antidepressants
    - Amitriptyline
    - Nortriptyline
    - Duloxetine
    - Venlafaxine
    - Lithium
  - Anti-epileptic medications
    - Divalproex
    - Topiramate
    - Valproate
  - Antihypertensive medications
    - Atenolol
    - Metoprolol
    - Nadolol
    - Propranolol
    - Timolol
    - Verapamil

        - Antiplatelet agents
        - Antipsychotics
        - Other headache management
            - Ergotamine
            - Intranasal capsaicin
            - Intranasal lidocaine
            - Lidocaine
            - Melatonin
            - Methylergonovine maleate
            - Metoclopramide
            - Non-steroidal anti-inflammatory drugs
            - Opioids
            - Botox
            - Dihydroergotamine
            - Triptans
            - Prednisone
            - Prochlorperazine
    - Other calcium channel blockers 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 (Bateman et al. 2013)
    - Visits with a neurologist (may indicate greater migraine severity)

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:
    - Presence of chromosomal anomalies (exclusion for analysis of malformations)
    - 25 most frequently occurring diagnoses recorded at the 3-digit level of the ICD-10 diagnosis code or Healthcare Cost and Utilization Project's Clinical Classifications Software

- Medication use:
  - 25 most frequently occurring medication classes used
- Health care utilization:
  - Count of office visits
  - Count and proportion of patients with at least 1 emergency department visit, and/or hospitalization
  - Number of distinct medications used, defined at the 10-digit level of the Generic Product Identifier coding system

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 and HIRD among pregnant women. Study feasibility will be monitored in the annual reports and comparative analyses will be initiated upon accrual of sufficient migraine patients exposed to galcanezumab to detect at least a 2-fold difference in the risk of major congenital malformations with at least 80% power.

On the day galcanezumab was approved (27 September 2018), the HIRD researchable population was 52% female, had a median age of 41 (interquartile range: 25 to 57), and members lived in more than 40 different states: 37% in the South, 25% in the Midwest, 23% in the West, and 15% in the Northeast. There were 12,136,652 reproductive-aged (15 to 49 years) female patients with at least 1 claim in the HIRD prior to galcanezumab launch, 461,415 of whom had a migraine diagnosis code (ICD-10 G43 code) during this period (prior to galcanezumab launch). These 461,415 women contributed a total of 2,104,744 (2.1 million) enrollment years (Median: 3.92 years, interquartile range: 2.06 to 5.74 years) by the galcanezumab launch date.

In 2018, there were 2069 (0.15%) women ages 15 to 49 years in the HIRD with a diagnosis of cluster headache. Based on preliminary data, we expect that the use of galcanezumab in patients without migraine will be rare. Among 6614 women ages 15 to 49 years in the HIRD with at least 1 dispensing of galcanezumab from January 2018 through January 2020 and no diagnosis of chronic cluster headache (n=28), only 75 (1.1%) had episodic/unspecified cluster headache and 377 (5.1%) had neither migraine nor cluster headache in the year prior to treatment initiation. 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.

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 evaluable galcanezumab mother-infant pairs and 1800 comparators gives a total study size of about 2230 linked pregnant women and infant pairs. In order to identify 430 evaluable galcanezumab-exposed mother-infant pairs, we would need to observe approximately 925 exposed pregnancies by the end of 2026 assuming that approximately 62% of pregnancies will end in a live birth and 70% to 75% of infants will successfully link to their mother. The actual number of exposed pregnancies needed to identify 430 evaluable galcanezumab-exposed mother-infant pairs may vary, especially as early spontaneous abortions may not come to medical attention. This could elevate the proportion of observed pregnancies that result in a live birth.

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 1800 unexposed pregnant women. Live birth and mother-infant linkage will not be required to support analysis of this outcome.

Table 1 describes the minimum detectable risk ratios for the target sample sized (430 galcanezumab-treated pregnant women and 1800 unexposed pregnant women) based on the maternal outcome of pre-eclampsia, retaining the same assumptions of a 4:1 ratio of comparator: galcanezumab, a z-alpha of 1.96, and 80% power.

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[a]
Major malformations	3%	2.00
Hypertension in pregnancy	4%	1.84
Pre-eclampsia	3%	2.00
Eclampsia	1%	2.95
Recognized spontaneous abortions	20%	1.31
Stillbirths	1%	2.95
Elective terminations	17%	1.35
Preterm delivery	10%	1.49
Low birthweight	9%	1.52
Small for gestational age infants	9%	1.52

[a] Power calculations were conducted using the Stata "power twoproportions" procedure to solve for minimum detectable relative risk as a proxy for our anticipated birth prevalence ratios based on z-alpha = 1.96, 80% power, 1720 comparator and 430 galcanezumab subjects (matched in a 4:1 ratio), and outcome prevalence in the reference group as indicated in the table above.

Medical records will be requested for all members of the galcanezumab migraine cohort and primary comparator cohort, and for a sample of other cohorts. All primary outcomes will be adjudicated based on medical records obtained. Given that not all patients will have medical record data available, we expect that the complete case sensitivity analysis may be underpowered. We will, however, validate and assess performance characteristics of the algorithms used in claims data to identify study outcomes, and will perform quantitative bias analysis to formally describe the potential impact of outcome misclassification on the appropriately powered main study results.

As of 31 May 2020, there were 15,333 patients with at least 1 dispensing of galcanezumab in the HIRD of whom 85% were female. Median age at first dispensing was 45 years, but 64% fell in the 15 to 49 age range. Of these patients, there were 18 (0.12%) exposed to galcanezumab before or during pregnancy. For purposes of this preliminary approximation, galcanezumab exposure was defined as a dispensing occurring no more than 14 months (ie, 9 months to account for rough duration of pregnancy and 5 months to account for the long half-life of galcanezumab) prior to a live birth. The strategy used to update this feasibility assessment will be refined in future years when exposure assessments/analyses are conducted per this study protocol.

The HIRD currently contains approximately 14.3 million currently active health plan members with both medical and pharmacy coverage in any given year, representing approximately 4.3% of the US population. Given the observed proportion of galcanezumab exposures resulting in an exposed pregnancy and current product uptake forecasting, we expect to accrue patients as shown in CCI over the study time period.

CCI

These preliminary estimates suggest accrual of 106 exposed pregnancies by 2026. However, the proportion of galcanezumab users experiencing pregnancy after use in future years is uncertain and will be reviewed during uptake monitoring. It may grow as the product has been on the market for a longer time if those with persistent exposure become pregnant more often than our overview of new users suggests. Alternatively, the proportion of users with an observed pregnancy may decrease compared to what we have observed to date due to random error, changes in healthcare coverage over time, or changes in prescribing and counselling habits. Further, the HIRD may ultimately cover more than the assumed 4.3% of US galcanezumab users in a given year as galcanezumab use may be more common among those with commercial benefits than those with other forms of insurance.

Annual updates to the feasibility assessment will be made using full protocol cohort entry criteria throughout uptake monitoring. These assessments will be used to guide selection of additional databases as needed. The specific number and composition of additional databases will be determined based on actual accrual of galcanezumab-exposed pregnancies available for inclusion in the study at the point that analyses must be conducted to meet the planned timeline. If by the 2024 interim report extrapolation from product uptake through 2024 indicates that study size in 2026 will be below target, we will initiate a feasibility assessment to identify additional data

sources for inclusion in the study. It is estimated that feasibility assessment can be completed and additional data sources enrolled within 2 years enabling the study to adhere to timelines for completion of Phase 2 comparative analyses by the final study report in December of 2027. Delaying selection of additional databases until product uptake is better established will enable a more targeted recruitment process informed by known rather than projected available sample size within additional data sources.

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, uptake monitoring will include conduct of the following analyses annually between 2019 and 2026. First, we will describe formation of the galcanezumab cohort and subcohorts based on (1) migraine, (2) episodic cluster headache, and (3) neither migraine nor cluster headache. The number of women included in each subcohort will be shown, as will attrition based on each study entry criterion. A brief table will describe women in each sub-cohort in terms of age at start of pregnancy, US region of residence, calendar year of cohort entry, timing of exposure, and mother-infant linkage. 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.

In Phase 2 descriptive analyses, for each interim report, we will first describe formation of the study cohorts. The number of women included in each subcohort will be shown, as will attrition based on each study entry criterion as specified in Section 9.2.2, Study Population. Those meeting all study entry criteria will be described in terms of the demographic, clinical, treatment and utilization characteristics described in Section 9.3.3, Covariates. Subgroups defined by baseline diagnosis of depression and hypertension (diagnoses that could potentially represent indications for use of comparator migraine prophylaxis medications) will be described. 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.

For each outcome (see Section 9.3.2, Outcomes), we will describe either the proportion of pregnancies affected (calculated as the number of events divided by the total number of pregnancies) 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. These rates will be unadjusted and not suitable for direct comparisons between galcanezumab and comparator groups prior to completion of formal comparative analysis. Stratified outcome categories will not be shown unless where there is less than 11 individuals

meeting the applicable outcome definition and less than 11 exposed pregnancies in the applicable stratum, noting that cell sizes less than 11 must be blinded due to patient privacy concerns.

9.6.2. Propensity Score-Adjusted Comparative Analyses

In Phase 2, comparative analyses to be conducted once the target sample size supporting analysis of major congenital malformations is reached, risk ratios or birth prevalence ratios (as applicable) and their 95% CIs will be calculated comparing galcanezumab-exposed pregnancies versus other comparator groups. Exposure will be assessed using the outcome-specific etiologically relevant exposure window (as defined in the Phase 2 SAP) with consideration of alternative windows in sensitivity analyses.

To control for confounding by indication, we will construct exposure propensity scores from applicable baseline characteristics (eg, excluding the 25 most frequently occurring diagnoses and medication used only to describe the cohort). The propensity score is the probability of being dispensed galcanezumab conditional on a set of observed covariates, and will be generated using logistic regression. Distinct propensity scores will be estimated for each planned comparison (ie, comparing galcanezumab versus each unique comparator group within the subset of patients to be included in analysis of each outcome). Cohort members whose propensity score is outside the region of overlap will be trimmed and excluded from further analysis. Estimates will be presented unadjusted and adjusted using a variable ratio propensity score match with up to 4 comparator cohort members per case.

Baseline characteristics between the cohorts will be evaluated for imbalances before any comparative outcome analyses begin, and covariates that remain imbalanced after adjustment (eg, retain a standardized difference greater than 10%) will be further adjusted by their inclusion in the outcome model. If differences between cohorts are substantial (eg, multiple covariates require additional adjustment), we will consider alternative approaches to adjustment. The study design will be modified if there is evidence that imbalances will hinder the interpretation comparative analysis results, and planned modifications will be documented as protocol amendments. No outcome analyses will be performed until the baseline assessment has occurred and the study design is finalized and approved.

Claims-based analyses will be performed for all primary and secondary outcomes and comparators. Additionally, analyses including combined data from claims and medical records will be performed for the primary analyses assessing the risk of pre-eclampsia and major congenital malformation, noting that medical record confirmed analyses may be required for additional outcomes in the event that claims-based analyses suggest an increased risk (eg, a statistically significant effect or a prevalence ratio greater than 2 where more than 10 outcomes have been identified). Small sample sizes may complicate interpretation of differences between primary and chart confirmed analyses for secondary outcomes that are rare. Missing data cannot be distinguished from negative indicator variables in claims (eg, it is not known whether a patient without any claims carrying an ICD-10 diagnosis code for diabetes is free from diabetes or is missing data on this covariate. We anticipate that missing data may arise where medical record review 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 missing variables, which could include case status or values for medical record based covariates shown in Section 9.3.3, Covariates. 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 1 medical record could not be obtained. Finally, performance characteristics identified in validation of study outcome algorithms within the galcanezumab-exposed and comparator cohorts will be used to inform quantitative bias analysis assessing the impact of outcome misclassification in the claims-based analysis.

9.6.3. Sensitivity Analyses

Planned sensitivity analyses will include the following. As cell counts less than 11 will be masked due to rules concerning patient privacy, stratified results will not be presented for those strata where less than 11 pregnant women are included in each exposure group.

- Depending on the frequency of outcomes, rates may be stratified by timing and duration of exposure. We will assess rates for all outcomes based on exposures during the whole pregnancy, based on exposure during each trimester, and based on possible exposures due to prepregnancy use without subsequent pregnancy exposure. Results will be discussed 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 prior to LMP, and during each trimester.
- Stratification based on the timing of medication dispensings plus days supply from 5 half-lives prior to the LMP through the end of pregnancy, including individuals whose latest dispensing plus days supply falls between
    - the LMP and the end of pregnancy
    - 30 days prior to the LMP and the end of pregnancy, and
    - 90 days prior to LMP and the end of pregnancy
- Addition of a washout period of 90 days prior to the main exposure window (5 half-lives prior to the LMP) for exclusion of study medications defining other cohorts to decrease the risk of exposure misclassification.
- Restriction of the study population to women with at least 12 months of health plan eligibility prior to the LMP (as sample size allows).
- Extension of baseline covariate ascertainment for chronic conditions to 90 days after the estimated LMP so that preexisting conditions documented at the first prenatal visit are captured.
- Revision of the list of known teratogens to include potential teratogens as referenced in Section 9.3.3, Covariates.

- Stratification by age at delivery, with age groups including 15 to 17, 18 to 39, and 40 to 49 years.
- For analyses of infant outcomes, revision of infant eligibility to (a) remove the 90-day health plan enrollment minimum duration, and (b) remove the requirement of mother-infant linkage.

Additional details of the planned analyses is 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. Study size will be assessed at several intervals including uptake monitoring and interim reports, and additional databases will be identified and incorporated if sample size requirements for primary analyses cannot be met using the HIRD alone. We do expect, however, that some stratified and sensitivity analyses (eg, subgroups of high or low maternal age) will have insufficient power. Where stratum sizes are low, we expect poor precision and possibly extreme or questionably interpretable results.

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 PPV and sensitivity of algorithms based on International Classification of Diseases, Ninth Revision, Clinical Modification codes have been studied for some outcomes, their performance has been mixed. For example, for major congenital malformations, a recent HealthCore study found wide variation in the performance of algorithms. While the PPVs for algorithms that detected specific major congenital malformations were generally very good (PPV greater than70%), 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 (Everage et al. 2013).

For some outcomes, high PPV has been reported with mixed findings on sensitivity. For example, International Classification of Diseases, Ninth Revision, Clinical Modification 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%) (Phiri et al. 2015). Studies from the Danish National Registry of Patients found a PPV of 97.40% (95% CI 92.70 to 99.50) for spontaneous abortion (Lohse et al. 2010) and 91.10% (95% CI 88.6 to 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 to 91) and 89% (95% CI 76 to 100) (Hure et al. 2015). 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 waiver of Health Insurance Portability and Accountability Act 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 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 (eg, 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 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 ethical review boards 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/Adverse Reactions

This is a noninterventional 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 prefilled 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.

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Annex 1. List of Standalone Documents

No.	Document Reference No.	Date	Title
1	N/A	N/A	I5Q-MC-B003 Study Code Lists

Annex 2. European Network of Centres for Pharmacoepidemiology and Pharmacovigilance 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:

[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,	☒	☐	☐	9

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
incidence rate ratio, 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:

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:

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:

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:

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:

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

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.6
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:

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:

Full details concerning data security and quality assurance procedures will be captured in the Statistical Analysis Plan. 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

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
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
12.2Does 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**
13.1Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	10
13.2Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3Have 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**
14.1Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	5

Comments:

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