PASS Information

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Research question and objectives	The purpose of the study is to prospectively evaluate maternal, fetal and infant outcomes through 12 months of age among women with migraine exposed to galcanezumab, a calcitonin gene-related peptide (CGRP) antagonist, during pregnancy, as well as in two galcanezumab-unexposed comparison groups. The primary objective is to compare the occurrence of major congenital malformations (main outcome), pregnancy outcomes, maternal pregnancy complications, infant outcomes at birth and infant events of interest up to 1 year post-delivery among women with migraine exposed to galcanezumab, with 1) women with migraine exposed to preventive migraine medications other than galcanezumab and other CGRP antagonists and 2) women with migraine not exposed to galcanezumab and/or any preventive migraine medications: • Congenital malformations (major and minor), separately • Pregnancy outcomes (recognized spontaneous abortions, elective terminations, stillbirths) • Maternal pregnancy complications (pre-eclampsia, eclampsia, hypertension in pregnancy)

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	• Infant outcomes (preterm birth, low birth weight and small-for-gestational-age births) • Infant events of interest (postnatal growth and development up to one year of age) Additional available published external data sources in patients/women with migraine and the general population for estimates of selected outcomes will be evaluated to contextualize observed outcome occurrences in the registry.
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2. List of Abbreviations

Term	Definition
AEs	Adverse events
AAN	American Academy of Neurology
CDER	Center for Drug Evaluation and Research
CDC	Centers for Disease Control and Prevention
CEDD	Corrected estimated date of delivery
CFR	Code of Federal Regulations
CGRP	Calcitonin gene-related peptide
CMA	Central monitoring associate
CRF	Case report form
EDC	Electronic data capture
ERB	Ethical Review Board
FDA	Food and Drug Administration
GPP	Good Pharmacoepidemiology Practice
HCP	Healthcare provider
IRB	Institutional Review Board
LBW	Low birth weight
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
NVSS	National Vital Statistics System
PLLR	Pregnancy and Lactation Labeling Rule
PMR	Post marketing requirement
RCC	Registry Coordinating Center
SAB	Spontaneous abortion
SAC	Scientific Advisory Committee

SAE	Serious adverse event
SAP	Statistical analysis plan
SAR	Suspected adverse reaction
SGA	Small-for-gestational-age
US	United States

3. Responsible Parties

Not applicable.

4. Abstract

- Title: A Prospective, Registry-based, Observational Study to Assess Maternal, Fetal and Infant Outcomes Following Exposure to Galcanezumab

  Version: 5.0

  Main author: PPD Syneos Health

- Rationale and background: Migraine prevalence is highest in women during childbearing years (Buse et al. 2013). There is often a medical need for preventive treatment of migraine during pregnancy, with treatment decisions based on clinical judgement of the benefits and the potential harms (Cassina et al. 2010). Pregnant women were not included in the galcanezumab clinical development program. The population of pregnant women treated with galcanezumab is therefore one which warrants further characterization, as effects on the fetus after exposure in utero are unknown. Accordingly, this study has been mandated by the Food and Drug Administration (FDA) to monitor pregnancy and infant outcomes.
- Research question and objectives: The purpose of the study is to prospectively evaluate maternal, fetal and infant outcomes through 12 months of age among women with migraine exposed to galcanezumab during pregnancy, as well as in two galcanezumab-unexposed comparison groups.

  The primary objective is to compare the relative occurrence of major congenital malformations (main outcome), fetal outcomes, maternal pregnancy complications, infant outcomes at birth and infant events of interest up to 1 year post-delivery among women with migraine exposed to galcanezumab, with 1) women with migraine exposed to preventive migraine medications other than galcanezumab and other CGRP antagonists (primary comparison group) and 2) women with migraine not exposed to galcanezumab and/or any preventive migraine medications (secondary comparison group)

  - Congenital malformations up to one year of age (major and minor malformations, separately)
  - Fetal outcomes (recognized spontaneous abortions, elective terminations, stillbirths)
  - Maternal pregnancy complications (pre-eclampsia, eclampsia, hypertension in pregnancy)
  - Infant outcomes at birth (preterm birth, low birth weight [LBW], small-for-gestational-age [SGA])
  - Infant events of interest up to one year of age (postnatal growth and development)

Additional available published external data sources in women with migraine and the general population for estimates of selected outcomes will be evaluated to contextualize observed outcome occurrences in the registry.

- Study design: This study is a prospective, observational, exposure-registration study in line with the current FDA guidance for designing and implementing pregnancy exposure registries (FDA 2019).
- Population: The study population will include pregnant women with migraine within the US who were treated with galcanezumab as part of routine care at any time during pregnancy or up to 5 months prior to last menstrual period (LMP), as well as pregnant women with migraine exposed to preventive migraine medications other than galcanezumab and other CGRP antagonists and pregnant women with migraine not exposed to galcanezumab and/or any preventive migraine medications.

  The minimum eligibility criteria required for enrollment are as follows:

  Inclusion:

  - Pregnant at the time of enrollment
  - Migraine as defined using the current International Classification of Headache Disorders-3 definition (Headache Classification Committee of the International Headache Society 2018, Annex 3)
  - Sufficient information to confirm eligibility for either the galcanezumab, exposed to preventive migraine medications other than galcanezumab or other CGRP antagonists, or not exposed to galcanezumab and/or any preventive migraine medications cohort
    - Galcanezumab cohort: at least one injection of galcanezumab (including date of injection) during the pre-pregnancy or pregnancy period (as defined in Section 9.3.1) without any other CGRP antagonist exposure during this time
    - Exposed to preventive migraine medications other than galcanezumab or other CGRP antagonists cohort: exposed to at least one preventive migraine medication other than galcanezumab or another CGRP antagonist during the pre-pregnancy or pregnancy period (as defined in Section 9.3.1)
    - Not exposed to galcanezumab and/or any preventive migraine medications during the pre-pregnancy or pregnancy period (as defined in Section 9.3.1)
  - Reporter (e.g., participant, maternal healthcare provider [HCP]) contact information to allow for follow-up
  - Permission to contact the patient's and her infant's HCPs
  - Patient informed consent to participate

Exclusion:

- Patients whose pregnancy has ended at the time of enrollment

- Variables:

  Galcanezumab Exposure: treatment with galcanezumab at any time during pregnancy or up to 5 months prior to LMP.

  Primary Comparison Group Exposure: Treatment with preventive migraine medications (taken for prevention of migraine) as identified by American Academy of Neurology (AAN) guidelines in 2012 and including any subsequent updates; currently including exposure to amitriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, nadolol, timolol, and onabotulinumtoxin A (Silberstein et al. 2012) at any time during pregnancy or up to 5 half-lives prior to LMP.

  Outcomes:

  - Congenital malformations: major and minor malformations, separately
  - Pregnancy outcomes: recognized spontaneous abortions, stillbirths, elective terminations
  - Maternal pregnancy complications: preeclampsia, eclampsia and hypertension in pregnancy
  - Infant outcomes at birth: preterm birth, LBW, SGA
  - Infant events of interest (up to one year of age): postnatal growth and development

- Data sources: The pregnant woman and appropriate members of her and her infant's health care team will serve as data reporters to the study. The study is strictly observational; patient care and treatment regimens will be determined by the treating HCP.

- Study size: The study aims to enroll a minimum of 420 prospectively enrolled evaluable (i.e., those for whom outcome of pregnancy including presence/absence of major congenital malformations was obtained) pregnant women with migraine and galcanezumab exposure who have live births, as well as two control groups consisting of 420 pregnant women with migraine exposed to preventive migraine medications other than CGRP antagonists who have live births and 420 women with migraine not exposed to galcanezumab and/or any preventive migraine medications who have live births.

- Data analysis: Once statistically feasible, compare the relative occurrence of maternal, pregnancy and infant outcomes among women exposed to galcanezumab with each of the two comparison groups.

  Demographic and baseline characteristics will be summarized with descriptive statistics for the galcanezumab-exposed group as well as for the two comparison groups.

Proportions and 2-sided, 95% confidence intervals will be calculated using the exact binomial distribution for prevalence of major congenital malformations among evaluable patients, preterm birth, LBW and SGA among patients with live births, preeclampsia, eclampsia and hypertension in pregnancy and infant growth and development through one year. Rates will be presented overall and stratified by timing of exposure.

- Milestones: The study will be open for enrollment April 2021. The estimated end of data collection is 30 November 2032, and the Final Study Report will be submitted 30 November 2033.

5. Amendments and Updates

All changes made in this amendment were implemented before the start of data collection.

Amendment or update Number	Date	Section of study protocol	Amendment or update	Reason
2	13-Mar-2020	Section 9.2.5.	Added Patient Payments (this change is retained in amendment version 3.0).	To improve patient recruitment and retention.
2	13-Mar-2020	Sections 4, 6, 9.2.1.	Updated study open for enrollment to April 2020 (this change is now superseded by a change in amendment version 3.0).	Additional time required for protocol amendment completion and IRB approval.
2	13-Mar-2020	Sections 4, 9.2.2., 9.2.4., 9.2.4.1., 9.5., 9.9.	Clarified unexposed to CGRP antagonist (with migraine) and general population (without migraine) cohorts and corrected unexposed to CGRP antagonist (with migraine) cohort definitions (this change is now superseded by changes in amendment version 3.0).	Improve clarity around enrolment of women into the comparator groups.
2	13-Mar-2020	Section 9.5.	Added number of women in the two unexposed control groups, unexposed to CGRP antagonist (with migraine) and general population (without migraine) and reference (this change is now superseded by changes in amendment version 3.0).	Improve clarity in number of women required to execute comparative analyses.
3	07-Jul-2020	Sections 4, 6, 9.2.1.	Updated study open for enrollment to Q4, 2020.	Allow time for FDA response to amended protocol and creation of SAP and CRFs.
3	07-Jul-2020	Sections 4, 8, 9.7.2.	The main outcome under the primary objective has been edited to “major congenital malformations”. The primary exposure time period for this outcome has been modified to the first trimester.	As requested by FDA
3	07-Jul-2020	Sections 4, 8	The study objective examining comparative analyses has been designated as primary.	As requested by FDA
3	07-Jul-2020	Sections 4, 9.2.2., 9.3.1., 9.4.3.	The galcanezumab exposure window has been edited to 5 half-lives (operationalized as 5 months) before LMP.	As requested by FDA

3	07-Jul-2020	Sections 4, 9.2.2., 9.3.1., 9.4.3.	LMP is now used to define pregnancy, trimesters of pregnancy, and pre-pregnancy exposure period for all groups.	As requested by FDA
3	07-Jul-2020	Sections 9.3.1., 9.4.1.	Galcanezumab dosage and, when applicable, discontinuation of use and reason for discontinuation will be collected.	As requested by FDA
3	07-Jul-2020	Sections 4, 9.3.1.	A complete list of migraine medications that will be considered as the exposure of interest for the comparator group has been added.	As requested by FDA
3	07-Jul-2020	Sections 4, 9.2.2.	Migraine has been added as an inclusion criterion for the primary study population.	As requested by FDA
3	07-Jul-2020	Sections 4, 8, 9.1., 9.2.4.1., 9.3.1.	Comparison groups have been modified as follows: Primary comparator: Women with migraine exposed to non-CGRP migraine preventives before or during pregnancy; Secondary comparator: Women with migraine not exposed to migraine preventives before or during pregnancy. The non-migraine comparator group has been removed.	As requested by FDA
3	07-Jul-2020	Section 9.7.2.1.	Women exposed to teratogens are no longer excluded from the registry. Separate analyses that include pregnancies with exposure to known teratogens and that exclude pregnancies with exposure to known teratogens will be performed when doing the analysis for the primary outcome of MCMs.	As requested by FDA
3	07-Jul-2020	Sections 4, 9.2.2.	Women under the age of 18 are no longer excluded from the registry.	As requested by FDA
3	07-Jul-2020	Section 9.2.2.	The definition of prospective has been expanded to include all pregnancies which have not ended. The definition of retrospective has been limited to only pregnancies that have ended.	As requested by FDA
3	07-Jul-2020	Sections 4, 9.2.2., 9.7.2.1.	The exclusion for abnormal prenatal test result prior to enrolment has been eliminated. Sensitivity analyses to address this patient subgroup have been added.	As requested by FDA

3	07-Jul-2020	Sections 9.3.2.2., 9.7.2.	Congenital malformations resulting from a chromosomal or genetic defect, or three or more conditional malformations have been removed from the primary analysis.	As requested by FDA
3	07-Jul-2020	Sections 4, 8, 9.7., 9.7.2.	Major congenital malformations and minor congenital malformations are now analysed separately.	As requested by FDA
3	07-Jul-2020	Sections 4, 9.3.2.1.	Ectopic pregnancy and molar pregnancy have been removed from the list of pregnancy outcomes.	As requested by FDA
3	07-Jul-2020	Section 9.3.2.1.	The definition of stillbirths has been modified to involuntary fetal loss occurring at ≥20 weeks of gestation, or, if gestational age is unknown, a fetus weighting ≥350 g (instead of ≥500 g).	As requested by FDA
3	07-Jul-2020	Sections 4, 8, 9.3.2.6., 9.3.2.7., 9.3.2.8.	Eclampsia, low birth weight (<2500 g), length, weight, head circumference, and the CDC's Developmental Milestones have been added as additional study outcomes.	As requested by FDA
3	07-Jul-2020	Sections 9.3.3.1., 9.4.1.1.	Covariate list revised to include migraine severity and frequency, worsening of migraine during pregnancy, thyroid abnormalities, congenital uterine abnormalities, infectious diseases, and indicators of health-seeking behavior.	As requested by FDA
3	07-Jul-2020	Sections 9.2.1., 9.4.1.2., 9.4.1.3., 9.4.5.	Additional maternal and infant assessments have been added.	As requested by FDA
3	07-Jul-2020	Section 9.5.	Sample size calculations have been modified to assume a 15% dropout rate and a 62% live birth rate.	As requested by FDA
3	07-Jul-2020	Section 9.5.	Power calculations for all secondary outcomes have been added.	As requested by FDA
3	07-Jul-2020	Section 9.7.2.1.	A sensitivity analysis based on different cut points of exposure has been added.	As requested by FDA
3	07-Jul-2020	Section 9.7.2.	An additional analysis for MCMs has been added that includes those detected from post-mortem examination of pregnancies with non-live birth outcomes.	As requested by FDA
3	07-Jul-2020	Section 9.7.	Additional detail on calculation of prevalence for all secondary outcomes has been provided.	As requested by FDA

3	07-Jul-2020	Section 9.4.2.	Additional detail on the handling of missing data has been provided.	As requested by FDA
3	07-Jul-2020	Section 9.2.3.	Additional detail on retention efforts have been provided.	As requested by FDA
3	07-Jul-2020	Section 9.4.2.	Additional detail on handling of lost-to-follow-up cases has been provided.	As requested by FDA
3	07-Jul-2020	Section 9.2.3.	Additional pregnancy awareness activities (including social media) have been added.	As requested by FDA
4	02-Oct-2020	Section 9.7.2.1.	An additional sensitivity analysis in women of advanced maternal age (>35 years of age and >45 years of age) has been added.	As requested by FDA
4	02-Oct-2020	Section 9.4.4.	Major congenital malformations will be adjudicated by a panel of two independent reviewers, comprised of qualified SAC members, with a third adjudicator in the event of a tie.	As requested by FDA
4	02-Oct-2020	Section 9.2.2.	Clarification that retrospectively reported pregnancies will be captured and assessed through the Lilly pharmacovigilance system.	As requested by FDA
4	02-Oct-2020	Section 9.5.	Additional detail on the power calculations has been provided.	As requested by FDA
4	02-Oct-2020	Section 9.7.2.	Addition of a propensity score-based stratified analysis.	As requested by FDA
5	Please see approval on front page	Section 9.5, Table 2	Sample size calculations revised based on the two sample test	As requested by FDA
5	Please see approval on front page	Section 9.7.2, 9.7.2.1	Statistical methods added for comparative analysis, including a propensity score-based stratified analysis	As requested by FDA
5	Please see approval on front page	Section 9.7	A. “Comparative analyses for the primary study objective will be performed for all data annually” has been revised to “Descriptive analyses will be performed for all data annually.” B. “For the primary study objective, analyses of relative occurrence of the study outcomes for the galcanezumab exposure compared to the two comparator groups pair-wise comparisons will be performed once statistically feasible” has been revised to remove “pair-wise comparisons.”	As requested by FDA

5	Please see approval on front page	Section 4, 6, 9.2	Start of data collection date updated. to “by April 2021”	To allow time for FDA approval of protocol and start-up activities.

6. Milestones

Milestone	Planned date
Start of data collection	April 2021
End of data collection	30 November 2032
Interim reports	Annually beginning 30 November 2021, ending 30 November 2031
Final report of study results	30 November 2033

7. Rationale and Background

Migraine is a recurrent headache disorder characterized by painful attacks lasting 4 to 72 hours 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 migraine to chronic migraine. Chronic migraine and episodic migraine are part of the spectrum of migraine disorders, but they are distinct clinical entities as classified by International Classification of Headache Disorders–3rd edition (ICHD 2018). In the United States (US), the prevalence of self-reported migraine and severe headache was 15.3% over a 3-month period (Burch et al. 2018). Migraine disproportionately affects women of childbearing age and is among the top 5 reasons for emergency department visits. Globally, migraine is ranked second as a cause of disability expressed as years lived with disability (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017).

Galcanezumab is a humanized IgG4 monoclonal antibody that binds CGRP and prevents its biological activity without blocking the CGRP receptor. Elevated blood concentrations of CGRP have been associated with migraine attacks (Durham et al. 2008). Three placebo-controlled phase-III 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) (Skljarevski et al. 2018, Stauffer et al. 2018, Detke et al. 2018). Emgality™ (galcanezumab), a once-monthly, subcutaneous 120 mg injection, with a 240 mg loading dose, which has a half-life of 27 days, has received approval from the FDA for the preventive treatment of migraine in adults and marketing authorization from European Commission for the prophylaxis of migraine in adults who have at least 4 migraine days per month.

As is standard, pregnant women were not included in the clinical development program; however, a number of pregnancies occurred in women treated with galcanezumab in the clinical trials: PPD

Embryo-fetal development studies conducted in rats and rabbits at exposures up to 29 times the highest proposed clinical dose of 300 mg revealed no evidence of harm to the developing fetus and there were no effects on survival, growth, sexual maturation, behavior, or reproduction in offspring exposed to galcanezumab in utero and through lactation at exposures up to 16 times the highest proposed clinical dose of 300 mg in the prenatal and postnatal development study in rats.

The current nonclinical data and the low number of pregnancy outcomes 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. 2013) during typical childbearing years. There is often a medical need for preventive 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 post-authorization setting and thus, further study is warranted.

Reviews of studies evaluating pregnancy outcome in women with migraine generally conclude that migraine, treated or untreated, probably has no effect on most pregnancy outcomes, including risk of congenital anomalies (MacGregor 2012; Menon and Bushnell 2008). Women with migraine have been reported to be at increased risk of developing hypertensive disorders such as pre-eclampsia in pregnancy compared to women without migraine (Banhidy et al. 2007; Facchinetti et al. 2009) which is associated with an increased risk of low birth weight (preterm birth, small for gestational age infant) (Adeney et al. 2005, Simbar et al. 2010, Facchinetti et al. 2009). In the migraine population, more severe migraine, defined by greater frequency and intensity, is associated with increased prevalence of cardiovascular comorbidity and comorbid affective disorders such as anxiety and depression (Chen et al. 2012; Goulart et al. 2014). Another challenge for evaluation of pregnancy, maternal, and fetal/infant outcomes is the known association of some prophylactic migraine medications with congenital malformations and other study outcomes. Therefore, careful selection of comparison populations of women with migraine treated with preventive migraine medication is needed to accurately contextualize event rates.

This prospective, registry-based, observational study to assess maternal and fetal outcomes following exposure to galcanezumab will fulfill a post marketing requirement (PMR) requested by the FDA's Center for Drug Evaluation and Research (CDER) and is designed to evaluate pregnancy outcomes as well as maternal, fetal and infant events of interest among women exposed to galcanezumab during pregnancy. The design and outcomes are chosen following the FDA request, the FDA draft guidance on postapproval pregnancy safety studies (FDA, 2019), and experience from other pregnancy studies.

8. Research Question and Objectives

The purpose of the study is to prospectively evaluate fetal, maternal and infant outcomes through 12 months of age among women exposed to galcanezumab during pregnancy, as well as in two galcanezumab-unexposed comparison groups.

The primary objective is to compare the occurrence of major congenital malformations (main outcome), fetal outcomes, maternal pregnancy complications, infant outcomes at birth and infant events of interest up to 1 year post-delivery among women with migraine exposed to galcanezumab, with 1) women with migraine exposed to preventive migraine medications other than galcanezumab and other CGRP antagonists and 2) women with migraine not exposed to galcanezumab and/or any preventive migraine medications:

- Congenital malformations (major and minor, separately)
- Fetal outcomes (recognized spontaneous abortions, elective terminations, stillbirths)
- Maternal pregnancy complications (pre-eclampsia, eclampsia, hypertension in pregnancy)
- Infant outcomes (preterm birth, LBW and SGA births)
- Infant events of interest (postnatal growth and development up to one year of age)

Additional available published external data sources in women with migraine and the general population for estimates of selected outcomes will be evaluated to contextualize observed outcome occurrences in the registry.

9. Research Methods

9.1. Study Design

This study is a prospective, observational, exposure registry of US women with migraine exposed to galcanezumab during pregnancy. Two comparison groups will also be enrolled: 1) women with migraine exposed to preventive migraine mediations other than galcanezumab or other CGRP antagonists and 2) women with migraine not exposed to galcanezumab and/or any preventive migraine medication. Additional available published external data sources in women with migraine and other population-based surveillance data will be evaluated to contextualize the registry findings.

The study is designed according to the current FDA guidance for designing and implementing pregnancy exposure registries (FDA 2019), and is strictly observational.

9.2. Setting

This study is US based.

9.2.1. Study Period

The study will be open for enrollment April 2021. The data collection process for each participant will begin at enrollment (during pregnancy), and follow-up will occur at the end of the first trimester (approximately 13 weeks' gestation), end of the second trimester (approximately 27 weeks' gestation) and/or at pregnancy outcome (delivery or early termination). The first and second trimester pregnancy follow-ups may not be applicable for women who enroll late in pregnancy. If a live birth is reported, the Registry conducts follow-up at 2, 4, 6, 9 and 12 months of age.

An annual interim study report, reviewed by the Scientific Advisory Committee (SAC), will be submitted to CDER beginning November 2021. The Interim Report summarizes the status and the cumulative data, current to the most recent annual data cutoff period. The estimated end of data collection is 30 November 2032. The last annual report will be submitted November 2031 and the final report will be submitted November 2033.

9.2.2. Study Participants

The study population will include pregnant women with migraine within the US who were treated with galcanezumab as part of routine care at any time during pregnancy or up to 5 months prior to LMP, as well as pregnant women with migraine exposed to preventive migraine medications other than CGRP antagonists and pregnant women with migraine not exposed to galcanezumab and/or any preventive migraine medications. Women in all three groups can be exposed to acute (symptomatic) migraine medications during or before pregnancy. Eligible pregnant women may self-enroll or voluntarily be enrolled by their HCP. Enrollment should occur as early in pregnancy as possible, preferably before any prenatal testing has occurred.

Enrollment and data collection will be coordinated through the Registry Coordinating Center (RCC). The minimum eligibility criteria required for enrollment are as follows:

Inclusion:

- Prospective (i.e. a pregnancy reported while the pregnancy is ongoing)
- Migraine, as defined using the current International Classification of Headache Disorders-3 definition (Headache Classification Committee of the International Headache Society 2018, Annex 3):
- Sufficient information to confirm eligibility for either the galcanezumab, exposed to preventive migraine medications other than galcanezumab or other CGRP antagonists, or not exposed to galcanezumab and/or any preventive migraine medication cohorts
    - Galcanezumab cohort: at least one injection of galcanezumab (including date of injection) during the pre-pregnancy or pregnancy period (as defined in Section 9.3.1) without any other CGRP antagonist exposure during this time,
    - Exposed to preventive migraine medications other than galcanezumab or other CGRP antagonists cohort: exposed to at least one preventive migraine medication other than a CGRP antagonist during the pre-pregnancy or pregnancy period (as defined in Section 9.3.1)
    - Not exposed to galcanezumab and/or any preventive migraine medication during the pre-pregnancy or pregnancy period (as defined in Section 9.3.1)
- Reporter (e.g., participant, maternal HCP) contact information to allow for follow-up
- Permission to contact the patient's and her infant's HCPs
- Patient informed consent to participate

Exclusion:

- Retrospective (i.e., a pregnancy reported after the pregnancy has ended). Retrospectively reported pregnancies will be captured and assessed through the Lilly pharmacovigilance system.

9.2.3. HCP and Patient Awareness and Retention Strategies

Study enrollment is open to all eligible pregnant women; however, a number of strategies will be employed to increase likelihood of enrollment. Registry awareness approaches may include, but are not limited to, the following:

- Product label to include registry contact information adhering to FDA's Pregnancy and Lactation Labeling Rule (PLLR)
- List the registry on FDA's listing of pregnancy registry site (https://www.fda.gov/science-research/womens-health-research/list-pregnancy-exposure-registries)

- List the registry on various pregnancy focused organizations websites (e.g., ACOG, Society for Maternal Fetal Medicine (SMFM) listing of registries)
- List the registry on Syneos Health's Active Pregnancy Registries web page
- Medical journal advertising and/or direct to physician advertising
- Outreach to treating/reporting HCPs (headache/migraine specialists, neurologists, internists, family practice, obstetrician/gynecologists) and patients including an announcement of the registry in appropriate organization newsletters targeting both healthcare providers and patients (professional societies such as American Headache Society, American College of Obstetricians and Gynecologists (ACOG), patient advocacy groups)
- Scientific presentations and publications
- Use of social media
- Registry-specific website with information on registry enrollment criteria, detail on how to enroll and a patient "request to be contacted" form
- Outreach to Lilly contracted physicians with information on the registry
- Plan to equip Lilly field medical employees with information on the registry to share with HCPs

A robust multi-pronged retention plan will be implemented to ensure that an adequate number of pregnant women remain in the registry. Specifics of patient retention strategies, contingency plans to obtain follow-up information, methods to track follow-up rates over time and implementation steps to improve follow-up if expected follow-up rates are not met will be addressed (FDA, 2019). Efforts will focus on participating HCPs, including the use of dedicated reporters to improve retention rates, reimbursement for time, and processes to reduce the burden of data collection. Alternate contact information is collected for the patient and multiple attempts to obtain the follow-up information are in place. Additionally, patients will be compensated for their participation at two data collection time points – Enrollment and Pregnancy Outcome – in order to keep the Registry top of mind and aid in prompting her and her infant's health care providers to submit data at the requested time points.

9.2.3.1. Dedicated Reporters

An active dedicated reporter model will be used to assist with patient identification. This strategy will entail reaching out to migraine/headache providers and obstetrician/gynecologists in a broad variety of settings. A recruitment strategy will target HCPs that are known to treat headache/migraine as well as pregnancy providers. A dedicated reporter is a healthcare professional (prescribing/treating/reporting physician) that agrees to actively enroll all eligible patients who provide consent among their patient population. Dedicated reporters are not considered site investigators. They follow the centralized Institutional Review Board (IRB) approval for the overall registry. By committing to actively identify and report all eligible consenting patients in their care, they substantially contribute to the enrollment and number of evaluable (i.e., those for whom pregnancy outcome and congenital anomaly assessment is

obtained) women in the analysis. Written assurance is required of all dedicated reporters that they agree to adhere to the set conditions.

Dedicated reporters are a subset of total HCP reporters contributing to the registry. They are identified based on their anticipated eligible patient population, which might include targeted outreach organizations (e.g. American Headache Society, ACOG), academic medical centers, and others identified as likely prescribers of galcanezumab to women of reproductive age. Migraine may be treated by neurologists, internal medicine, family practice, or ob/gyn physicians. Intelligence on prescribing practices will be utilized where available to assist with identifying potential reporters.

9.2.4. Selection of Comparison Data

The registry will enroll two comparator groups: women with migraine exposed to preventive migraine medications other than CGRP antagonists and women with migraine not exposed to galcanezumab and/or any preventive migraine medications. This study will also use external published migraine and population-based data to provide context for the events observed in the galcanezumab cohort.

9.2.4.1. Internal Comparison Groups

The registry will attempt to enroll 420 evaluable women with migraine exposed to preventive migraine medications other than galcanezumab or other CGRP antagonists with live births and 420 evaluable women with migraine not exposed to galcanezumab and/or any preventive migraine medications with live births.

The reporting HCP for the galcanezumab-exposed pregnant women will be asked to identify and enroll a pregnant woman meeting the criteria for each of the comparison groups. Should the reporting physician not be able to identify an eligible patient for either comparison groups, the comparison groups could be supplemented with self-referred pregnant women who suffer from migraines. Additionally, the subset of dedicated reporting physicians (see above) can serve as a source of both comparison groups of pregnant migraine patients, treated with preventive migraine medication(s) other than CGRP antagonists and not exposed to galcanezumab and/or any preventive migraine medications.

Reporting maternal HCPs, including the group of dedicated reporting physicians (see above) can serve as referral sources of pregnant women with migraine. An additional supplemental approach, if needed, will be to invite enrolling women in the galcanezumab exposed group to "refer a friend" with migraines who is pregnant to participate.

9.2.4.2. External Data Sources

The use of published external data sources such as studies and general population estimates will be evaluated to contextualize the findings of the registry. The published final results of the Sumatriptan, Naratriptan, Treximet Pregnancy Registry (Ephross and Sinclair 2014) represent a readily available external non-CGRP antagonist exposed historical pregnant migraine population. However, it is important to note that only major birth defects apparent at birth were captured, as

infants were not followed up to one year of age. In addition, while some pregnancy outcomes including spontaneous abortions, fetal death/stillbirths and elective terminations were collected, other outcomes of interest such as pre-eclampsia, eclampsia, hypertension during pregnancy, preterm birth, LBW, SGA, and postnatal growth/development through one year of age were not collected.

Published results from the Metropolitan Atlanta Congenital Birth Defects Program (MACDP) for congenital malformations, as well as published data for other outcomes of interest (e.g. the CDC National Vital Statistics System (NVSS) for the US prevalence of preterm birth (Martin et al. 2019) can serve as supplemental background information. While the MACDP is considered to be the standard coding criteria for congenital malformation evaluation, there are well known limitations such as geographic representation and patient demographics that are not ideally reflective of the whole US population. External studies are still useful to allow the assessment of generalizability of this study's findings and any other future study findings.

Should other newly available or newly identified appropriate supplemental migraine and/or population-based comparison data from the literature and other sources, such as other pregnancy registries or observational studies become available, these will be evaluated as possible additional data to contextualize further the results of this study.

9.2.5. Patient Payment

Nominal compensation will be offered to patients for completing enrollment and once pregnancy outcome is received.

9.3. Variables

9.3.1. Exposure(s) of Interest

The exposure of interest is treatment with galcanezumab for migraine at any time during pregnancy or up to 5 months prior to LMP. Any injection of galcanezumab within 5 months prior to the LMP is considered pregnancy exposure due to its long half-life. Data will be collected regarding dates of treatment, dosage and number of doses, as well as discontinuation, if applicable, and reason for discontinuation. The trimester of exposure will also be captured.

The primary comparison group will include only women with migraine exposed to preventive migraine medications (being taken for the prevention of migraine) other than galcanezumab or other CGRP antagonists during pregnancy and/or five half-lives before pregnancy. The preventive migraine medications included are those identified by American Academy of Neurology (AAN) guidelines in 2012 and will include those identified in any subsequent AAN updates. Current comparator medications include exposure to amitriptyline, venlafaxine, divalproex, topiramate, valproate, atenolol, metoprolol, propranolol, nadolol, timolol, and onabotulinumtoxin A (Silberstein et al. 2012) at any time during pregnancy or up to 5 half-lives prior to LMP.

The secondary internal comparison group will be comprised of women with migraine not exposed to galcanezumab or any other preventive migraine medications during pregnancy and/or sufficient time before pregnancy based on the drug's half-life.

Treatment is not under control of the study but administered solely at the discretion of the pregnant woman's treating HCP and as part of routine clinical care. Only data that are routinely recorded in the course of usual care among women treated with galcanezumab during pregnancy will be collected.

9.3.2. Congenital Malformations, Pregnancy Outcomes, Maternal Pregnancy Complications, Infant Outcomes and Infant Events of Interest

9.3.2.1. Pregnancy outcome

Each **pregnancy outcome** will be reported as one of the following:

- Live birth: an infant born alive
- Stillbirth: involuntary fetal loss occurring at 20 weeks' gestation or greater, or if gestational age is unknown, a fetus weighing 350 g or more
- Recognized spontaneous abortion (SAB): fetal death or expulsion of products of conception prior to 20 weeks' gestation. Terminology may include missed abortion, incomplete abortion, and inevitable abortion.
- Elective termination: voluntary interruption of pregnancy, including pregnancy termination that occurs electively, to preserve maternal health, or due to abnormalities

Maternal death will be assessed on a case-by-case basis to determine if it is an evaluable or non-evaluable patient.

9.3.2.2. Congenital Malformations

The study defines and codes congenital malformations with criteria specified by CDC MACDP (CDC 2018). A major congenital malformation (MCM) is defined as any major structural or chromosomal defect in live-born infants, stillbirths or spontaneous losses equal to or greater than 20 weeks' gestation or electively terminated pregnancies of any gestational age. This definition is consistent with the CDC MACDP definition. Minor abnormalities that do not significantly affect health and development, and normal variants are ascertained only among those who also have a major defect (Correa et al. 20007).

The study conforms to the CDC MACDP guidelines; it disqualifies as defects those findings that are present in infants born at less than 36 weeks of gestation and which are attributable to prematurity itself (such as patent ductus arteriosus, patent foramen ovale, or inguinal hernias). The CDC MACDP classification includes chromosomal and genetic defects. Congenital malformations resulting from a chromosomal or genetic defect, will be excluded from the primary analysis, but will be included in a sensitivity analysis. Though these defects are not

likely to contribute to a risk for a medication exposure, the study includes these defects to maintain this consistency with the CDC MACDP.

Live-born infants with only transient or infectious conditions or with biochemical abnormalities will be classified as being without reported congenital malformations unless there is a possibility that the condition reflects an unrecognized defect. Detected and reported transient or infectious conditions or biochemical abnormalities in infants without reported MCMs and defects that are excluded by the CDC guidelines will be noted in an appendix in the study reports.

The Registry will systematically collect information on major structural and chromosomal defects that are apparent at birth and noted through infant age one year: congenital malformation(s) and details, if noted, type of congenital malformation(s) if applicable, attribution to drug therapy, and other factors that might have contributed to the outcome.

If a major congenital malformation is reported, other data of interest can be collected through targeted follow-up.

9.3.2.3. Preterm birth

An infant born at gestational age <37 weeks

9.3.2.4. Low birthweight

An infant weighing <2500 g at birth

9.3.2.5. Small for gestational age

Birthweight ≤10th percentile for gender and gestational age using the NCHS pediatric growth curves for full term infants. Prenatal growth curves will be used for preterm infants.

9.3.2.6. Maternal pregnancy complications

Pre-eclampsia, eclampsia, hypertension in pregnancy (see Annex 4 for definitions)

9.3.2.7. Infant outcomes

Gestational age, birth weight, sex, length, weight, head circumference

9.3.2.8. Infant events of interest

Dates of follow-up evaluation, current age of infant, length, weight, head circumference, developmental milestones monitored per the CDC's Developmental Milestones *https://www.cdc.gov/ncbddd/actearly/milestones/index.html*

9.3.3. Other Variables

Other variables will be collected for the description of baseline characteristics of the study population or to determine gestational age or the presence of possible confounding factors.

9.3.3.1. Maternal characteristics

Age, ethnicity, race, occupation, BMI, migraine severity and frequency, worsening of migraine during pregnancy, indicators of health-seeking behaviors (number of OB/GYN visits in the last two years)

9.3.3.2. Paternal characteristics

Age

9.3.3.3. Prenatal data

LMP, estimated date of delivery (EDD), corrected estimated date of delivery (CEDD), singleton or multiple pregnancy

9.3.3.4. Prenatal tests

Name of test, date of test, result

9.3.3.5. Obstetrical history

Previous pregnancies (singleton/multiple) and their outcomes (live births, stillbirths, SABs, elective terminations), births with congenital malformations, family history of congenital malformations

9.3.3.6. Co-morbid medical conditions

Diabetes, hypertension, depression, thyroid abnormalities, congenital uterine abnormalities, infectious diseases

9.3.3.7. Concomitant medications

Prescriptions and over-the-counter medications including migraine treatment

9.3.3.8. Substance use

Alcohol, tobacco, and illicit drug use

9.4. Data Sources

The pregnant woman and appropriate members of her and her infant's health care team will serve as data reporters to the study. The study is strictly observational; patient care and treatment regimens will be determined by the treating HCP. There will be no additional laboratory tests or assessments required as part of this study. Any additional tests during pregnancy will only be done on the basis of the pregnancy needs and as decided on by the treating HCP. Only data recorded as part of routine care will be collected. The following table provides a summary of data that will be collected at specific time points and the source of data. [Further details on the operational definitions are provided under 9.4.1, 9.4.2 and 9.4.3.]

Table 1. Summary of patient follow-up and data collection timepoints

Information Requested	Maternal Contact (Patient)		Maternal HCP Contact			Infant HCP Contact		Evaluator
	Enrollment	Outcome[e]	Registration	Interim Follow-Up (1^{st}, 2^{nd} trimester)	Outcome Follow-Up	Follow-Up (at birth)[f]	Follow-Up (2, 4, 6, 9 and 12 months)	Targeted Follow-Up
Reporter Information and Permissions								
Report source, permission to contact HCP (for pregnant patient), pediatrician, and alternate patient contact information as applicable	✓	✓[e]	✓					
Maternal Information								
Maternal characteristics (age, ethnicity, disease status)	✓		✓					
Maternal prenatal information (LMP, EDD, CEDD, prenatal test results & timing)	✓		✓	✓[a]	✓[a]			
Obstetrical history (maternal and paternal)	✓		✓					✓[d]
Family history (maternal and paternal)	✓		✓					
Galcanezumab, or other migraine preventive, therapy (indication for use, dates of administration) (maternal/paternal as appropriate)	✓[g]		✓	✓[a, g]	✓[a, g]			
Concomitant medications (Rx, OTC, dietary supplements, herbals), during pregnancy (dosage, routes, start/stop date of administration), recreational/illicit drug, alcohol and tobacco use during pregnancy	✓		✓	✓[a]	✓[a]			

Maternal concurrent medical conditions	✓		✓	✓[a]	✓[a]			
Outcome of Pregnancy Information								
Pregnancy status	✓		✓	✓	✓[a]			
Outcome information (fetal loss, live birth, gestational age, weight)				✓[b]	✓	✓[f]		
Birth defect noted, description, attribution, if applicable				✓[b]	✓			
Other factors that may have contributed to outcome (etiology)				✓[b]	✓			✓[d]
Infant Follow-up Information								
Length, weight, head circumference							✓[ac]	
Birth defect noted, description, attribution, if applicable						✓[cf]	✓[ac]	
Other factors that may have contributed to outcome (etiology)						✓[cf]	✓[ac]	✓[d]
CDC Developmental Milestones						✓[f]	✓[ac]	

[a] Obtain updated information since the previous contact.

[b] Obtain this information if outcome has occurred.

[c] Collect only for live birth outcomes.

[d] Collect information not previously obtained, to facilitate the characterization of the fetal loss and/or birth defect(s).

[e] Contact to obtain Medical Information Release Form for Pediatrician if not previously obtained.

[f] Collect only if unable to collect at birth from Maternal HCP contact.

[g] Applicable for galcanezumab exposed group only.

9.4.1. Overview of data collection process

9.4.1.1. Information Collected at Enrollment

After applicable patient informed consent is obtained from the eligible woman, the reporter will complete the *Registration Form* and submit it to the RCC.

Reporter Information

- Contact information for the patient, as well as alternate contact information, such as a permanent address and/or next of kin
- HCP reporter contact information
- Medical Information Release Forms (Pediatric Medical Release Form may be collected around time of EDD if unknown at enrollment)

Maternal and Paternal Information

- Maternal and paternal demographics
- LMP
- EDD determined from LMP
- CEDD (e.g. by ultrasound) if available
- Singleton or multiple pregnancy
- Prenatal tests (diagnostic or screening) performed, date of test(s), and findings including the identification of congenital anomalies

Maternal Obstetrical History

- Number of previous pregnancies (singleton or multiple)
- Outcome of all previous pregnancies
- History of offspring with congenital anomalies
- Maternal and paternal history of congenital anomalies

Maternal Galcanezumab Exposure (in case of self-enrollment of a galcanezumab-exposed pregnancy, to be provided initially by the pregnant woman at study enrollment and confirmed by the treating HCP)

- Galcanezumab injection(s), including date(s), indication for use, dosage, and (if applicable) discontinuation and reason for discontinuation

Other Conditions and Exposures

- Concurrent maternal conditions, including migraine (type, aura status, severity and frequency, worsening of migraine during pregnancy)

- Concomitant medications taken during pregnancy, including migraine treatments
- Tobacco, alcohol, and illicit drug use during pregnancy

Indicators of health-seeking behavior

- Number of OB/GYN visits in the last two years

9.4.1.2. Information Collected at Pregnancy Follow-up

Around the end of the first trimester, end of the second trimester and in the month of the EDD, the *Interim Pregnancy Follow-up Form* and *Pregnancy Outcome Form* (respectively) will be requested from the obstetric HCP or the patient, if applicable. For subjects that enroll late in pregnancy, the End of First Trimester and/or End of Second Trimester follow-up(s) might not be applicable. In the month of the expected date of delivery, the Registry prompts the pregnant patient's HCP to complete the ***Pregnancy Outcome Form***. The patient is also contacted to provide authorization for medical release for the baby's pediatrician (if not previously obtained).

Follow-up(s) at End of First and Second Trimester

Pregnancy Status

- Updates to expected date of delivery (i.e., CEDD)
- Subsequent prenatal tests (diagnostic or screening) performed and findings including the identification of congenital anomalies
- Pregnancy complications (preeclampsia, eclampsia, hypertension during pregnancy)
- Details of pregnancy outcome if pregnancy is no longer ongoing (see Follow-up at Pregnancy Outcome)

Other Exposures during pregnancy

- Concomitant medications (including migraine medications)
- Tobacco, alcohol, and illicit drug use during pregnancy

Follow-up at Pregnancy Outcome

Pregnancy Outcome

- Pregnancy outcome (live birth, stillbirth, SAB, elective termination, ectopic, molar)
- Date of outcome of pregnancy
- Gestational age at outcome
- Fetal/infant characteristics: gender, birth weight, length, weight, and head circumference
- Congenital malformation(s) and potential contributing factors
- For a fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss

9.4.1.3. Information Collected at Pediatric Follow-up

Timing of Pediatric Follow-Up

If a live birth occurs, and the mother has not already provided permission at enrollment, she is asked to give consent for the infant's pediatrician to provide follow-up information. If consent is obtained, the pediatrician completes the ***Pediatric Follow-Up Form*** at 2, 4, 6, 9 and 12 months of age.

Pediatric Follow-up Form

Infant Outcome

- Date of follow-up evaluation
- Current age of infant
- Current length, weight and head circumference of infant
- Developmental milestones per CDC's Developmental Milestones
- Congenital malformation(s) and details, if noted
- Type of congenital malformation(s) if applicable, attribution to galcanezumab drug therapy, and other factors that might have contributed to the outcome

Targeted Follow-up after report if an event of interest

If there is a congenital malformation, in order to properly characterize the event, additional information may be requested from the reporting HCP on the *Targeted Follow-up Form*:

- Details of the congenital malformation
- Etiology
- Maternal infections of relevance to congenital malformations
- Other information considered relevant by the HCP
- Specific questions requested by the congenital malformation evaluator

9.4.2. Follow-up process

Attempts to Obtain the Follow-Up Information

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. Three subsequent attempts, as necessary, will be made every two weeks via various modes of communication, e.g., phone, fax, email, mail. If the missing follow-up data is essential to characterize the outcome or event and there is still no response from the provider, a final communication will be sent indicating the case is lost to follow-up. If this communication prompts a response from the HCP or the requested data is later received, the case will be re-opened and assessed for evaluability. If, at any point in the follow-up process, the reporter specifically indicates that the patient is lost to follow-up, no further attempts will be made, but an attempt to obtain information on the cause of loss to follow-up will be made.

Follow-Up Process for Clarification of Information

For critical data points, if there are outstanding questions, discrepancies between forms, or missing data, the appropriate reporter will be contacted for clarification. Three subsequent attempts, as necessary, will be made every two weeks. If no further information is obtained on an otherwise evaluable case, the discrepant information in the data fields may be left blank or identified as "unspecified" or "missing". On a case-by-case basis, qualified study staff may make a determination on discrepant information (e.g., determination of partially illegible word or illogical year) in accordance with electronic Case Report Form Completion Guidelines (eCRGs).

9.4.3. Operational Exposure Definition

When a pregnant woman enrolls in the study, she will be asked when she was last treated with galcanezumab. When a pregnant woman is enrolled by her HCP, the HCP will provide this information. The pregnant woman will then be asked to provide a medical release that allows the RCC to confirm galcanezumab treatment with the appropriate source. Reported galcanezumab injection at any time during pregnancy (from five months prior to LMP until pregnancy outcome) will constitute a fetal exposure. Exposures that occur in the 5 months prior to LMP will be categorized as a first trimester exposure. Galcanezumab exposure will be further categorized by earliest trimester of exposure.

For this study, gestational weeks will be estimated from the most reliable EDD as reported by the HCP or the pregnant woman. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester will be considered to begin at week 14 after LMP, and the third trimester at week 28. If there is a discrepancy between gestational age calculated from LMP and reported gestational age, the HCP will be asked to verify the data.

9.4.4. Operational Outcome and Event Definition and Identification Process

All pregnancy outcome and maternal/infant events of interest variables will be provided by the treating or obstetric HCP and the infant's pediatrician. In case no data on the pregnancy outcome can be obtained from the HCP, the pregnant woman will be asked to provide information on the pregnancy outcome. The HCP will be asked to describe any congenital malformations observed in the infant or fetus at birth and will also be asked to report the gestational age and birthweight, as described in the medical records. These last two variables will be used to calculate preterm birth (gestational age <37 weeks at birth), LBW (<2500 g) and SGA (birth weight ≤10th percentile for gender and gestational age) in live births.

A teratologist/geneticist will review all reported congenital malformations and classify them using the CDC's MACDP system as specified in 9.3.2. As adjudication of major congenital malformation cases can be complex, there will be an adjudication panel of two independent reviewers, comprised of qualified SAC members, with a third adjudicator in the event of a tie.

The reviewers and method of assessment will be the same for both the exposed and comparator groups and the reviewers will be blinded to the exposure status (FDA 2019).

This review includes identification of specific aspects of the case for further inquiry from the reporter(s), clarification and classification of the defect(s) reported (in accordance with the classification conventions of the MACDP (CDC, 2018) and a classification system developed to increase the ability to generate potential safety signals (Scheuerle and Tilson, 2002). The evaluator may assess a report as "pending further information" if more information is needed to determine the etiology of the defect. However, if no further information is received despite repeated attempts, the evaluator makes an assessment based upon available information.

Once the exposure status blinding is broken following the review, the SAC review includes definition of the potential relevance of timing of exposure to the event(s) reported –'temporality assessment'.

The SAC assessment includes the following:

- The SAC may assess a report as "pending further information" if more information is needed to determine the temporality. However, if no further information is received despite repeated attempts, the SAC makes an assessment based upon available information.

The assessments of temporality with the Registry drug exposure are classified as one of the following:

- Pending
- The development of this defect and the timing of the exposure to drug cannot rule out a possible association
- No temporal association
- Unable to assess
- Defect with known cause, temporality may be irrelevant
- Pathogenesis of this defect has yet to be defined specifically enough to assess temporality
- Not a defect

9.4.5. Operational Variable(s) Definition

As is indicated in 9.4, for women who self-enroll, maternal characteristics will be provided by the pregnant woman at study enrollment. After the woman provides consent and medical release for her HCP(s) to provide data, the therapeutic or obstetric HCP will provide prenatal data (LMP, EDD, and CEDD), prenatal test data (test, date of test, and result), obstetrical history (previous pregnancy outcomes, births with congenital malformations, and family history of congenital malformations), concomitant medical conditions, concomitant medications, and alcohol, tobacco, and illicit drug use. At pregnancy outcome, the obstetric HCP will provide pregnancy outcome

data (live birth, stillbirth, SAB, or elective termination) and infant outcome data (gestational age, length, birth weight, head circumference and gender). In case data on the pregnancy outcome cannot be obtained from the HCP, the pregnant woman will be asked to provide information on the pregnancy outcome. The infant's HCP will provide information at 2, 4, 6, 9 and 12 months of age.

9.4.6. Scientific Advisory Committee

An independent SAC will be established to oversee the scientific affairs of the study, including its ongoing monitoring. A charter for SAC activities, roles and responsibilities and meeting frequency will be established at study start. The SAC will comprise recognized experts including (but not limited to) the fields of teratology, epidemiology, maternal and fetal medicine, as well as migraine treatment. The SAC will meet regularly to review the accumulated body of data from the study, including review and classification of reported MCMs and other events of interest, and to carry out any actions required, including review and interpretation of interim data analyses and reports and publications of study data. The SAC may meet on ad hoc occasions if indicated. In addition to the above activities, the SAC will contribute to the design and implementation of strategies to heighten awareness of the study.

9.5. Study Size

The study aims to enroll a minimum of 420 prospectively enrolled evaluable pregnant women with galcanezumab exposure who have live births, as well as two control groups consisting of 420 pregnant women with migraine exposed to preventive migraine medications other than CGRP antagonists who have live births and 420 pregnant women with migraine not exposed to galcanezumab and/or any preventive migraine medication who have live births. Assuming a baseline major malformation frequency of 2.78% in the MACDP (Correa et al. 2007), approximately 420 galcanezumab exposed live births and 420 corresponding comparison group live births are needed to have 80% power to detect a 2.56-fold difference in the baseline risk of major malformations (2.78%).

Assuming 15% loss to follow-up, it is anticipated that approximately 495 patients with galcanezumab exposure as well as 495 patients in each of the two control groups will need to be enrolled. Research indicates that approximately 83% to 95% of pregnancies enrolled in pregnancy exposure registries result in a live birth (Covington et al. 2010), resulting in a lower estimate of approximately 520 and an upper estimate of 595 live births in each group, assuming 15% lost to follow-up only. Using a more conservative 62% live birth rate in addition to the 15% loss to follow-up, 797 evaluable pregnant women in the galcanezumab exposure as well as 797 patients in each of the two comparison groups will need to be enrolled to yield 420 live births in each group.

A two-sided two-sample Fisher's exact conditional test was used to calculate the study sample size needed based on the prevalence rate of major congenital malformations, and power for other outcomes. Statistical level of significance used in the sample size calculation was 0.05. Procedure Power in SAS (version 9.2 or higher; SAS Institute, Cary, NC) was used to perform the sample size calculation.

Power estimates for MCMs and other study outcomes are provided in Table 2. For the outcomes for which the number of pregnancies is the denominator in calculating the prevalence rate, a 62% live birth rate is assumed (420 evaluable live births corresponds to 677 evaluable pregnancies).

Comparative analyses for the 2033 final report will be executed and the precision reported for each outcome (i.e. the -fold difference that can be detected given 80% power for MCM and the sample size at that time).

Table 2. Power for detecting 2.56-fold difference in study outcomes (assuming 62% live birth rate)

Outcome	Estimated prevalence in general population	Power of detecting 2.56-fold difference in prevalence with 420 evaluable live births (677 evaluable pregnancies)
Major malformations*(Correa et al. 2007)	2.78%	80.0%
Minor malformations*(Holmes and Wesgate 2011)	4%	93.4%
Hypertension in pregnancy (Umesawa and Kobachi 2017)	4%	99.3%
Preeclampsia (Ananth et al. 2013)	3%	96.7%
Eclampsia (Abalos et al. 2013)	1%	51.8%
Recognized spontaneous abortions (Rossen et al. 2018)	20%	>99.9%
Stillbirths (Say et al. 2006)	1%	6051.8%
Elective terminations (Jatlaoui et al. 2019)	17%	>99.9%
Preterm delivery* (Martin et al. 2019)	10%	>99.9%
Low birthweight* (Martin et al. 2018)	9%	>99.9%
Small for gestational age infants* (Martin et al. 2018)	9%	>99.9%

* Number of live birth is the denominator

9.6. Data Management

Patient data are recorded on data forms. RCC study personnel are responsible for the integrity of the data (that is, accuracy, completeness, legibility, and timeliness) reported to Lilly.

All patients who provide consent to release information and who fulfil the study entry criteria will be included in the analyses. For those patients who are lost to follow-up, or who drop out of the study, the analyses will include all data up to the point of their last data collection.

9.6.1. Data Processing

Data for this prospective observational safety study will be managed with an electronic data capture (EDC) platform, Medrio, which is US Code of Federal Regulations (CFR) 21 CFR Part 11 compliant. Only the variables described in the protocol under section 9.3 will be solicited and entered in the EDC. Participants and/or their HCPs will provide data over the phone or by

completing a paper case report form (CRF), which can be submitted to the RCC via mail, email or fax. The data will be reviewed by a registry central monitoring associate (CMA) associate for correctness and completeness and entered into the database.

9.6.2. Software and Hardware

Data analyses will be performed using the statistical software program, SAS (version 9.2 or higher; SAS Institute, Cary, NC).

9.7. Data Analysis

Descriptive analyses will be performed for all data annually. For the primary study objective, analyses of relative occurrence of the study outcomes for galcanezumab exposure compared to the two comparator groups will be performed once statistically feasible.

The summary statistics for continuous and categorical variables to be used will be specified in the statistical analysis plan (SAP) but may include means, standard deviations, medians, minimums, maximums, percentiles, n's, percentages and 2x2 tables to reflect the number of events of interest per pregnancy outcome.

The study will identify the number of cases for major and minor congenital malformations (separately), pregnancy outcomes, maternal pregnancy complications, and infant outcomes and events of interest as described in Section 8. Proportions/prevalences of these outcomes will be calculated with 95% confidence intervals from the total number of pregnant women, or live births as appropriate. Stratification may be done by earliest trimester of exposure, maternal age and other relevant variables, where applicable.

9.7.1. Analysis of Demographics and Baseline Characteristics

Demographic and baseline characteristics will be summarized with descriptive statistics for the galcanezumab exposed, exposed to preventive migraine medications other than CGRP antagonists and not exposed to galcanezumab and/or any preventive migraine medications groups. Characteristics can be compared with the exposed group to assess potential differences. These data will be reviewed for potential confounding factors that could affect the interpretation of comparisons of study outcome data with that of comparator data. Further details will be included in the SAP.

9.7.2. Statistical Methods

Bivariate stratified analyses and propensity score-based stratified analysis will be used for comparative analysis, overall and within subgroups. All stratified analyses and subgroup analyses will include point estimates and 2-sided 95% confidence intervals, calculated using the exact binomial distribution for prevalence of major congenital malformations among evaluable patients, preterm birth, LBW and SGA among evaluable patients with live births, preeclampsia, eclampsia and hypertension in pregnancy and infant growth and development through one year for each of the galcanezumab exposed, and two comparison groups. Additionally, two comparisons for the difference in the prevalence of each outcome between the cohort of women exposed to galcanezumab and two comparator cohorts will be tested using Fisher's exact test.

Most structural defects have their origins in the first trimester of pregnancy, the period of organogenesis. In addition to overall prevalence of observed MCMs, the analysis of MCMs will be stratified by trimester of earliest exposure to galcanezumab. The prevalence of combined MCMs reported to the study will be calculated as a proportion with the number of observed MCMs as the numerator and the number of live births as the denominator, among women with first trimester exposure. The primary analysis for MCMs will be based on first trimester exposure, and a second analysis of MCMs following second trimester exposure will be done.

The primary analysis will include MCMs among live births, with an additional analysis for MCMs including those detected/reported from postmortem examination of pregnancies with non-live birth outcomes. Live birth will be used as the denominator for each: this method also is a conservative approach and allows comparison of outcomes with the CDC MACDP. The prevalence of observed MCMs in exposed cases will be compared with the most recent reported prevalence of the CDC MACDP. Additionally, if a sufficient sample size is attained for each trimester exposure group, it may be possible to compare the prevalence of MCMs among exposures to galcanezumab in the first trimester versus those in the second or third trimester combined, in addition to the two comparison groups.

Only congenital malformation cases meeting the CDC MACDP criteria for a major defect will be included in the primary analysis. In the absence of a major malformation, minor defects, defined as structural changes that pose no significant health problem in the neonatal period and tend to have limited social or cosmetic consequences for the affected individual, do not constitute a MCM according to the CDC MACDP classification; therefore, they will be analyzed separately and not included in the primary analysis. Congenital malformations resulting from a chromosomal or genetic defect, will be excluded from the primary analysis, but will be included in a sensitivity analysis.

The prevalence of recognized SAB, stillbirths, elective terminations, preeclampsia, eclampsia and hypertension in pregnancy will be calculated as proportions, with the number of pregnancies as the denominator. The prevalence of preterm births, LBW and SGA, as well as postnatal growth and development, will be calculated as proportions, with the number of live births as the denominator. Because MCMs and multiple gestation pregnancies are often associated with preterm birth, LBW and SGA, these infants will be excluded from analyses of these outcomes and will not be counted in the numerator or denominator when prevalence is determined.

The prevalence of outcomes in exposed cases will be compared with that in the two comparison groups, as well as with published data.

For this study, gestational weeks are estimated from the most reliable EDD as reported by the HCP. If a CEDD is provided by the HCP, it will be used instead. The date of conception will be calculated as the most reliable EDD minus 38 weeks. If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester will be considered to begin at week 14 after LMP, and the third trimester, at week 28. If there is a discrepancy between gestational age calculated from LMP and reported gestational age, the HCP will be asked to verify the data.

9.7.2.1. Methods to Control for Confounding and Effect Modification

For analyses of associations between exposure/comparison groups and outcomes, confounding and effect modification will be evaluated. A detailed description of these analyses will be available in the SAP. Potential confounders/effect modifiers may include, but are not limited to, the following:

- Maternal age
- Previous pregnancy outcomes (e.g. MCMs, stillbirths)
- Pregnancy complications (e.g. preterm labor, preeclampsia and hypertension in pregnancy, eclampsia, placental abruption)
- Comorbidities (e.g. diabetes, hypertension, depression, others)
- Concomitant exposures (e.g. medications (including migraine treatments), alcohol, tobacco)
- Paternal demographics (e.g. age)

Subgroup Analyses, Stratification and Sensitivity Analyses

Analyses will be stratified by trimester of exposure and other subgroups of interest, potentially including gestational age at enrollment and maternal age. In addition to bivariate stratification, propensity score-based stratification will also be employed. The propensity score will be estimated from multinomial logistic regression with cohort (galcazumab exposed cohort, primary and secondary comparison cohort) as dependent variable, and demographic and maternal characteristics as independent variables. The propensity score used for stratification is the patient level probability of being in the galcazumab exposed cohort conditioned on demographic and maternal characteristics. SAS procedure Logistic with link function of mlogic will be used to estimate the propensity score.

Sensitivity analyses will be performed as well, as described below. Additional details on subgroup analyses, stratification and sensitivity analyses will be described in the SAP.

Separate analyses that include pregnancies with exposure to known teratogens and that exclude pregnancies with exposure to known teratogens will be performed when doing the analysis for the primary outcome of MCMs.

Because of the long half-life of galcanezumab and the wide exposure definition prior to LMP, a sensitivity analysis based on different cut points of exposure will be performed.

Sensitivity analyses will be performed on the following subgroups:

- Women of advanced maternal age (>35 years of age and >45 years of age)
- Women who enroll after 20-week ultrasound anatomy scans, regardless of prenatal testing results compared to enrollment prior to 20-week ultrasound anatomy scans
- Women who enroll after prenatal testing such as a fetal anatomy ultrasound, compared to enrollment prior to such testing, and
- Women who enroll after prenatal diagnosis of any major structural defect

9.8. Quality Control

9.8.1. Validation

Ensuring that the data obtained are of high quality will be an ongoing, multi-step process involving both automatic programming of edit checks for critical data variables in the Medrio EDC system as well as visual review for completeness, logic, consistency, and accuracy by the RCC staff. As recommended in regulatory guidance documents, CRFs are carefully designed to ensure data quality and integrity. All patient-reported data will be verified by the appropriate HCP, where possible.

9.8.2. Record Retention

The RCC will retain all study records required by Lilly and by the applicable regulations in a secure and safe facility for the duration of the study. The RCC will consult a Lilly representative before disposal of any study records, and must notify Lilly of any change in the location, disposition, or custody of the study files. Study records with redacted patient identifiers will be transferred to Lilly at the end of the study. Documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained by Lilly for a period of five years in accordance with Good Pharmacoepidemiology Practice (GPP) guidelines. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements.

9.9. Limitations of the Research Methods

Since participation in the study will be voluntary, the included patients may not be representative of the overall US pregnant women population. Because early prenatal testing is so prevalent, it would be difficult to achieve adequate numbers of prospectively enrolled pregnant women if all pregnancies with prior prenatal testing are excluded from the analysis. The primary analysis will include all pregnancies enrolled regardless of prenatal testing. Pregnancies enrolled after prenatal testing but prior to pregnancy outcome, as well as those who enroll after prenatal diagnosis of any major structural defect will be evaluated in sensitivity analyses. As reporting of pregnancies is totally voluntary, it is possible that even in prospectively reported cases, potential bias could exist. For example, high-risk pregnancies (i.e. one that threatens the health or life of the mother or her fetus) or low-risk pregnancies may be more likely to enroll. Baseline characteristics will be evaluated to identify whether such selection bias may have played a role.

Those pregnancies that have reached EDD, but for which pregnancy outcome information was unobtainable after 4 attempts (1 initial followed by 3 subsequent attempts at 2-week intervals), will be considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in individual reporting patterns, it is not possible to assess with any certainty what impact potential biases from losses to follow-up may have on the analysis. However, efforts at comparing some of the characteristics of each group may be conducted in an attempt to address this potential source of bias. Following the MACDP convention, calculation of MCM prevalence will exclude fetal losses (SABs, elective terminations, stillbirths, etc.) for which no MCMs have been

diagnosed as they may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data collection form attempts to obtain information on MCMs detected at the time of the outcome. However, the reporting physician may not know the condition of the aborted fetus.

Migraines are associated with some baseline pregnancy risks and comorbidities. It will be important to compare the galcanezumab-exposed, and the two comparison groups for population differences that may potentially result in differential pregnancy outcomes and the introduction of bias.

An important potential limitation of this pregnancy registry is the possibility of lower than expected enrollment. This can result either because galcanezumab is not being prescribed to women who are or may become pregnant, or because exposed women are not being reported/enrolled into the registry. If enrollment projections are not being met, it will be important to understand why and to identify additional strategies for increasing registry enrollment.

Requiring women to be pregnant at the time of enrollment means that spontaneous abortions occurring early in pregnancy may not be included in the registry. Only recognized spontaneous abortions occurring after enrollment will be captured. It is important to enroll women as early in pregnancy as possible and before pregnancy outcome has occurred to maximize the number of prospective enrollments into the registry.

Potential biases related to the composition of the two comparison groups will need to be considered. The preventive migraine medications other than CGRP antagonists treated migraine controls may have been treated with other prescribed migraine therapies (e.g. anti-epileptic medications including topiramate, tricyclic anti-depressants, or beta-blockers) which themselves can be associated with pregnancy outcomes, maternal pregnancy complications, and/or maternal comorbidities associated with infant outcomes. If statistically feasible, the impact of type of migraine therapy in this control group will be assessed in sensitivity analyses. Additionally, there may be differences in migraine severity between the two comparison groups. If the number of women in the registry is small, baseline differences between the exposure cohorts may not be overcome, limiting the ability of the registry to provide meaningful conclusions.

10. Protection of Human Subjects

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. In addition, regardless of local law, all primary data collection observational studies will be submitted to at least 1 independent body (for example, IRB) per country for review and to confirm that the study is considered non-interventional in that country. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

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

10.1. Informed Consent

Informed consent will be obtained for each study patient ≥18 years of age, who self-enrolls or is enrolled by her HCP. Parental consent and patient assent will be obtained for each study patient <18 years of age. As noted below, this study qualifies for a waiver of documentation of written informed consent. Participants will provide verbal consent under the waiver of written informed consent.

10.1.1. Waiver of Documentation of Written Informed Consent

The following US regulations indicate that waiver of written informed consent by the subject or the subject's legally authorized representative is appropriate for this study.

As stated in the US CFR 21 CFR 56.109 (and additionally in 45 CFR 46.117(c)(2)):

- "(c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:

- The IRB may, for some or all subjects, waive the requirement that the subject, or the subjects legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context.

- (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require the investigator to provide subjects with a written statement regarding the research."

11. Management and Reporting of Adverse Events/Adverse Reactions

The study personnel will capture in the electronic database all protocol-defined adverse events (AEs), including all associated fatal outcomes, occurring in temporal association with galcanezumab and comparator products that are under evaluation as defined in this protocol. The protocol-defined AEs for this study are specified in Section 9.3 Variables.

Pregnancy exposure does not meet the definition of an AE. However, it is collected per protocol and should be considered a protocol-defined AE. Because galcanezumab exposure in pregnancy is the primary protocol-defined inclusion criterion for this registry, these will not be considered AEs. All other AEs will not be actively collected due to lack of relevance to study outcomes. Protocol-defined adverse events will be summarized in the final study report.

Study personnel are requested to report any suspected adverse reactions (SARs) with Lilly products not under evaluation in this protocol or SARs with non-Lilly products to the appropriate party (for example, regulators or the marketing authorization holder) as they would in normal practice.

Study personnel are not obligated to actively collect AEs or serious adverse events (SAEs) in patients once they have discontinued from the study. However, if the study personnel learn of any SAE, including death, at any time after the patient has discontinued from the study and the event is considered reasonably possibly related to the Lilly product under evaluation, the study personnel must promptly notify Lilly.

11.1.1. Serious Adverse Events

RCC personnel will report to Lilly or its designee any protocol-defined SAE arising in temporal association with galcanezumab within 1 business day of awareness of the event via a sponsor-approved method. Reports received via telephone will be documented on a Telephone Contact Report and transcribed onto the appropriate field on the CRF and entered into the study EDC system by the CMA where possible.

A protocol-defined SAE is any AE from this study that results in one of the following outcomes:

- Death
- Initial or prolonged inpatient hospitalization
- A life-threatening experience (that is, immediate risk of dying)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect (i.e. congenital malformation)
- Or is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above.

11.1.2. Nonserious Adverse Events

The study personnel will report to Lilly or its designee any non-serious protocol-defined AE arising in temporal association with galcanezumab within one (1) business day of awareness of the event via the sponsor-approved method.

11.2. Product Complaints

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.

Complaints related to unblinded comparator drugs or concomitant drug/drug delivery systems are reported directly to the manufacturers of those drugs/devices in accordance with the package insert.

Investigators are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

Annual interim study reports, reviewed by the SAC, will be submitted to CDER beginning November 2020. The Interim Report summarizes the status and the cumulative data, including database line listings, are current to the most recent data cutoff period. The last annual report will be submitted November 2031, the estimated end of data collection is 30 November 2032 and the final report will be submitted November 2033.

The data may also be considered for reporting at scientific conferences or for publication in scientific journals.

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Annex 1. List of Standalone Documents

Not applicable.

Annex 2. ENCePP Checklist for Study Protocols

Not applicable.

Annex 3. Migraine Definition, International Classification of Headache Disorders-3

Migraine without aura: Recurrent headache disorder manifesting in attacks lasting 4–72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia.

Migraine with aura: Recurrent attacks, lasting minutes, of unilateral fully reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms.

Chronic migraine is further defined as headache occurring on 15 or more days/ month for more than three months, which, on at least eight days/month, has the features of migraine headache.

Headache Classification Committee of the International Headache Society, 2018

Annex 4. Preeclampsia and Hypertension in Pregnancy Definitions

Box 2. Diagnostic Criteria for Preeclampsia

Blood pressure

- Systolic blood pressure of 140 mm Hg or more or diastolic blood pressure of 90 mm Hg or more on two occasions at least 4 hours apart after 20 weeks of gestation in a woman with a previously normal blood pressure
- Systolic blood pressure of 160 mm Hg or more or diastolic blood pressure of 110 mm Hg or more. (Severe hypertension can be confirmed within a short interval (minutes) to facilitate timely antihypertensive therapy).

and

Proteinuria

- 300 mg or more per 24 hour urine collection (or this amount extrapolated from a timed collection) or
- Protein/creatinine ratio of 0.3 mg/dL or more or
- Dipstick reading of 2+ (used only if other quantitative methods not available)

Or in the absence of proteinuria, new-onset hypertension with the new onset of any of the following:

- Thrombocytopenia: Platelet count less than $100,000 \times 10^9$/L
- Renal insufficiency: Serum creatinine concentrations greater than 1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease
- Impaired liver function: Elevated blood concentrations of liver transaminases to twice normal concentration
- Pulmonary edema
  - New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms

Hypertension in Pregnancy: A systolic blood pressure 140 mm Hg or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation, in a woman with a previously normal blood pressure

ACOG 2019; Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy 2000