Observational Cohort Study of Exposure to Lasmiditan During Pregnancy (H8H-MC-B002)

Confidential Information

Protocol Electronically Signed and Approved by Lilly: approval date provided below

Approval Date: 14-Jan-2022 GMT

Post-authorization Safety Study (PASS) Information

Title	Observational Cohort Study of Exposure to Lasmiditan During Pregnancy
Study Identifier	H8H-MC-B002
Version identifier	Final (Version 1.0)
Date of last version	01-Oct-2021 (Draft Version 0.5)
EU PAS Register No:	NA
Active substance	Lasmiditan; ATC code: NO2CC08
Medicinal product(s):	Lasmiditan tablets 50mg, 100mg, 200mg
Product reference:	LY573144
Procedure number:	NA
Marketing authorization holder(s)	Eli Lilly and Company
Joint PASS	No
Research question and objectives	The primary objective is to estimate and compare the prevalence of composite major congenital malformations among pregnant women with migraine exposed during the first trimester to lasmiditan and unexposed comparator populations. The secondary objectives of this study are to estimate and compare prevalences of major congenital malformations (composite and individual), spontaneous abortions, stillbirths, preterm births, small-for-gestational-age infants, gestational hypertension, pre-eclampsia, and eclampsia among pregnant women with migraine exposed to lasmiditan and unexposed comparator populations anytime during pregnancy. This is a claims-based retrospective cohort study comparing pregnant women exposed to lasmiditan to three unexposed comparator populations: (a) pregnant women with migraine not exposed to lasmiditan. The following subgroups of pregnant women not exposed to lasmiditan will also be evaluated (a1) exposed to triptans and not gepants, and (a2) exposed to gepants and not triptans.
Country(ies) of study	United States
Author	PPD HealthCore, Inc.

Marketing Authorization Holder

Marketing authorization holder (MAH)	Eli Lilly and Company
MAH contact person	Lilly Global Patient Safety Pharmacoepidemiologist

1. Table of Contents

Section **Page**

List of Tables

Table **Page**

List of Annexes

2. List of Abbreviations

Term	Definition
AE	Adverse event
CGRP	Calcitonin gene-related peptide
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
HIRD	HealthCore Integrated Research Database
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision
ID	Identification
IPW	Inverse Probability Weight
IRB	Institutional review board
IQR	Interquartile range
LMP	Last menstrual period
MCM	Major congenital malformations
NDA	New Drug Application
NSAID	Non-steroidal anti-inflammatory drug
PHI	Protected Health Information
PMR	Post-marketing requirement
PR	Prevalence ratio
SAP	Statistical Analysis Plan
SGA	Small-for-Gestational-Age
US	United States

3. Responsible Parties

Name, degree(s)	Title	Affiliation	Address
PPD		Eli Lilly and Company	Lilly Corporate Center Indianapolis, IN 46285
PPD		HealthCore, Inc.	480 Pleasant St., Suite A100, Watertown, MA 02472
PPD		HealthCore, Inc.	123 Justison St, Suite 200 Wilmington, DE 19801

4. Abstract

Title: Observational Cohort Study of Exposure to Lasmiditan During Pregnancy

Rationale and background: Migraine is a disabling neurological disease characterized by recurrent episodes of severe headache accompanied by other symptoms including nausea, vomiting, sensitivity to light and sound, and vision disturbance. Migraine prevalence is highest in women during typical childbearing years (18-49 years). Most women who experience a migraine while pregnant use pharmaceutical intervention, often non-narcotic analgesics or triptans. These drugs do not offer relief in all cases and may be contraindicated in some patients, even if use during pregnancy may be safe. In October 2019, Food and Drug Administration (FDA) approved lasmiditan, a serotonin (5-HT) 1F receptor agonist for the acute treatment of migraine with or without aura in adults (new drug application [NDA] 211280). The approval included a post-marketing requirement ([PMR] 3728-6) to assess major congenital malformations, spontaneous abortions, stillbirths, preterm births, small-for-gestational-age infants, gestational hypertension, preeclampsia, and eclampsia in women exposed to lasmiditan during pregnancy compared to an unexposed control population.

Research question and objectives: The primary objective is to estimate and compare prevalence of composite major congenital malformations among pregnant women with migraine exposed during the first trimester to lasmiditan and unexposed comparator populations. The secondary objectives of this study are to estimate and compare prevalences of major congenital malformations (composite and individual), spontaneous abortions, stillbirths, preterm births, small-for-gestational-age infants, gestational hypertension, pre-eclampsia, and eclampsia among pregnant women with migraine exposed to lasmiditan and unexposed comparator populations anytime during pregnancy.

Study design: This is a claims-based retrospective cohort study comparing pregnant women exposed to lasmiditan to three unexposed comparator populations: (a) pregnant women with migraine not exposed to lasmiditan. The following subgroups of pregnant women not exposed to lasmiditan will also be evaluated (a1) exposed to triptans and not gepants, and (a2) exposed to gepants and not triptans. Comparator groups listed in (a1) and (a2) are subsets of the larger lasmiditan unexposed group.

Population: The source population for this study includes women of childbearing age in the HealthCore Integrated Research Database (HIRD) from 31 January 2020 to 31 December 2027.

Variables: Pregnant women treated with acute migraine medications will be identified using medical and pharmacy claims. Pregnancy outcomes will be identified in medical claims using prespecified criteria for each cohort. Covariates will be identified using enrollment data, pharmacy and medical claims and include demographic variables, obstetric variables (e.g., multifetal gestation, parity, prior miscarriage), gynaecologic comorbidities, cardiovascular, psychiatric, infectious, and other comorbidities, and use of other pharmaceuticals.

Data sources: This study will be conducted using the HIRD, which includes longitudinal medical and pharmacy claims data from health plan members across the United States (US).

Study size: To detect a prevalence ratio (PR) between treatment groups of 2.0 or higher with 80% power, given a potential 4:1 comparator:lasmiditan propensity score matching ratio, for major congenital malformations (composite), a minimum of 683 pregnant lasmiditan users will be needed. As lasmiditan penetrates the market, HealthCore will track patient accrual in the HIRD Patient accrual will be monitored annually and if not on track to reach a minimum of 683 pregnant women with migraine exposed to lasmiditan (minimum required for major congenital malformations analysis) by the end of the enrollment period (2027), options for extending the time needed for patient accrual or expanding the sample size by adding one or more data partners will be assessed.

Data analysis: Prevalence ratios and 95% confidence intervals will be calculated using propensity-score methods to balance covariates between treatment groups. Lasmiditan users will be compared separately to each comparator group.

Milestones: Planned start date of data collection will be 31 January 2022 with the planned submission of the Final Study Report by 31 December 2028.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestone	Planned date
Final Protocol[1]	11 January 2022
Start of data collection	31 January 2022
End of data collection	31 December 2027
Annual Interim Reports	31 December 2021 31 December 2022 31 December 2023 31 December 2024 31 December 2025 31 December 2026
Final report of study results submission	31 December 2028

1. The above timeline outlines the estimated timeframes.

7. Rationale and Background

Background

Migraine is a disabling neurological disease characterized by recurrent episodes of severe headache accompanied by other symptoms including nausea, vomiting, sensitivity to light and sound, and vision disturbance in a limited number of patients.[1] Migraine prevalence is highest in women during typical childbearing years, aged 18 to 49 years.[2] Women with a history of migraine may be more likely to experience adverse pregnancy outcomes, including preeclampsia and preterm birth.[3] Further, women who become pregnant can experience a migraine during pregnancy. If this occurs during the first trimester, patients may take migraine medications before they are aware of their pregnancy.

Treatments for migraine fall into two general categories: preventive medications and acute treatments. During pregnancy, preventive migraine drugs are recommended only for the most severe migraine patients,[4] while drugs for acute treatment are more common.[5] Importantly for claims-based studies, drugs indicated for the acute treatment of migraine are taken on an as-needed basis. Patients who fill a prescription for an acute drug, for example, may not take the drug until they have a migraine, which may not occur until days, weeks, or months later. In this way, as-needed drugs differ from preventive or maintenance medications.

Acute medications for migraine vary in their pregnancy safety profiles.[6] Acetaminophen, diphenhydramine, metoclopramide, and non-steroidal anti-inflammatory drugs (during the second trimester only) are considered safe for use during pregnancy. Triptans vary in their pregnancy safety profiles, with sumatriptan showing the most evidence supporting its safety during pregnancy.[4,6,7] Triptans do not provide relief for all patients, however, and may be contraindicated due to vasoconstrictive effect.[7,8]While the aforementioned drugs are generally considered safe for use during pregnancy,[4,6] two new classes of migraine relief drugs have recently emerged (ditans and gepants),[8-10] and their safety profiles for use during pregnancy are unknown.

In October 2019, the Food and Drug Administration (FDA) approved lasmiditan (REYVOW®) tablets for the acute treatment of migraine with or without aura in adults (new drug application [NDA] 211280). Following FDA approval, lasmiditan became commercially available in January 2020. Lasmiditan is a selective serotonin (5-HT) 1F receptor agonist that differs from triptans in that it binds more selectively and does not induce vasoconstriction.

Recently, FDA approved rimegepant and ubrogepant, both small molecule calcitonin gene-related peptide (CGRP) receptor antagonists, for acute treatment of migraine.[9,11] An additional gepant, zavegepant, is anticipated for FDA approval.[10] Like lasmiditan, gepants avoid the cranial vasoconstriction induced by triptans.[8] Gepants differ from monoclonal antibody CGRP inhibitors which are large molecules used for migraine prevention.[12]

Concerning the public health significance of studying the safety of migraine treatments taken during pregnancy, it appears that many women experience migraines during pregnancy and that most of these women take one or more medications for migraines. In a population-based cohort

study of 60,435 pregnant women conducted in 2009, 5.8% experienced migraine attacks during the first five months of pregnancy.[5] Of these women, 72.6% used a migraine drug. The most common migraine drugs taken by pregnant women were non-narcotic analgesics (54.1%) and triptans (25.4%).

Study Rationale

The 2019 FDA approval included a post-marketing requirement ([PMR] 3728-6). To meet this requirement, this study protocol describes an observational, post-marketing safety study to evaluate the risk of maternal, fetal, and infant outcomes resulting from exposure to lasmiditan during pregnancy.

8. Research Question and Objectives

The objectives of the present study are:

Primary objective:

- To estimate and compare the prevalence of composite major congenital malformations (MCM) in infants of women with a dispensing of lasmiditan 30 days prior to last menstrual period (LMP) and anytime during the first trimester of pregnancy compared to three unexposed comparator groups: (a) pregnant women with migraine not exposed to lasmiditan 30 days prior to LMP and anytime during the first trimester of pregnancy. The following subgroups of pregnant women not exposed to lasmiditan will also be evaluated (a1) exposed to triptans and not gepants 30 days prior to LMP and anytime during the first trimester of pregnancy, and (a2) exposed to gepants and not triptans 30 days prior to LMP and anytime during the first trimester of pregnancy.

Secondary objectives:

- To estimate and compare prevalences of MCM (composite and individual), spontaneous abortions, stillbirths, preterm births, small-for-gestational-age (SGA) infants, gestational hypertension, pre-eclampsia, and eclampsia in pregnant women with migraine exposed to lasmiditan anytime during pregnancy to three unexposed comparator groups: (a) pregnant women with migraine not exposed to lasmiditan. The following subgroups of pregnant women not exposed to lasmiditan will also be evaluated (a1) exposed to triptans and not gepants, and (a2) exposed to gepants and not triptans. Comparator groups listed in (a1) and (a2) are subsets of the larger lasmiditan unexposed group.
- To describe demographic characteristics, exposure to other medications during or before pregnancy, rates of pregnancy, maternal and infant outcomes among women with migraine exposed to lasmiditan and three unexposed comparator groups: (a) pregnant women with migraine not exposed to lasmiditan. The following subgroups of pregnant women not exposed to lasmiditan will also be evaluated (a1) exposed to triptans and not gepants, and (a2) exposed to gepants and not triptans. Comparator groups listed in (a1) and (a2) are subsets of the larger lasmiditan unexposed group.

9. Research Methods

9.1. Study design

This is a retrospective cohort study using data from administrative commercial insurance claims.

Tracking Uptake of Study Drugs and Feasibility Assessment

In order to facilitate comparative analysis, descriptive data for female users of lasmiditan, 16-44 years of age, as they accrue in the database, will be provided in annual interim reports. Annual Interim Reports will be provided for six years, with informal, interim updates taking place every six months during study team meetings. Each Annual Interim Report shall include: (a) the number of female lasmiditan, triptans, and gepants users in the HealthCore Integrated Research Database (HIRD), (b) the number of pregnant women exposed to study drugs, (c) user demographics, and (d) preliminary outcome frequencies. Lasmiditan is the first drug of its class and other drugs of this class may be introduced during the study period. To prevent potential exposure misclassification, market uptake will be monitored during the study period and any drug added to this class will be excluded from comparator groups.

Descriptive analyses will characterize females in the exposed and comparator groups regarding their demographics, number of pregnancies, distribution of types of migraine diagnosis, and frequency of dispensing.

For each year of the enrollment period and upon the completion of enrollment, HealthCore will report the frequency of International Classification of Diseases, Tenth Revision (ICD-10) codes for each of the following pregnancy outcomes in pregnant women exposed to lasmiditan: MCMs, spontaneous abortions, stillbirths, preterm births, SGA infants, gestational hypertension, pre-eclampsia, and eclampsia. For MCMs, ICD-10 codes will be taken from the European Surveillance of Congenital Anomalies classification guide,[13] which provides code lists and classifications for major and minor congenital anomalies.

During the data collection period, the literature will be monitored for validation studies of ICD-10 codes for the eight pregnancy outcomes and covariates to be assessed during the comparative analysis. ICD-10 codes for these outcomes differ from the International Classification of Diseases, Ninth Revision (ICD-9) codes in both content and structure. ICD-10 is relatively new and algorithms using these codes are unavailable in the published literature. HealthCore and Eli Lilly are concurrently conducting a post-approval pregnancy study for preventive migraine drug galcanezumab (PMR 3498-3). The galcanezumab study includes medical record validation for MCMs identified in the HIRD. The study team will use the literature and the findings from the galcanezumab study to inform the best approach for identifying MCMs for the present study.

If uptake is not on track to reach a minimum of 683 pregnant women exposed to lasmiditan by the end of 2027 (monitored annually) (see Section 9.5 Study Size), then additional data sources will be assessed for possible inclusion in the study.

Comparative Analyses

This analysis includes maternal and infant outcomes comparing pregnant women with migraine exposed to lasmiditan to pregnant women with migraine not exposed to lasmiditan.

This study will include four cohorts of pregnant women with migraine:

- **Exposed:** Pregnant women with migraine treated with lasmiditan (exposed or "treated" group).
- **Comparator 1:** Pregnant women with migraine not exposed to lasmiditan (these women may be exposed to other acute migraine medications including triptans and gepants).
- **Comparator 2:** Pregnant women with migraine not exposed to lasmiditan or gepants, exposed to triptans. No other migraine-specific medications during the exposure assessment period. A list of migraine-specific medications can be found in Appendix 1 Tables 1-4.
- **Comparator 3:** Pregnant women with migraine not exposed to lasmiditan or triptans, exposed to gepants. No other migraine-specific medications during the exposure assessment period. A list of migraine-specific medications can be found in Appendix 1 Tables 1-4.

In order to conduct several of the sensitivity analyses, a cohort of pregnant women without migraine not exposed to lasmiditan or any other migraine medication during the baseline period or anytime throughout pregnancy will be evaluated.

Prevalence ratios (PRs) and 95% confidence intervals will be calculated using propensity-score methods to balance covariates between treatment groups. Lasmiditan users will be compared separately to each comparator group. Each outcome listed below will be assessed in separate models.

The eight outcomes are:

1. Major congenital malformations (composite and individual)
2. Spontaneous abortion
3. Stillbirth
4. Preterm birth
5. Small-for-gestational-age
6. Gestational hypertension
7. Preeclampsia
8. Eclampsia

9.2. Setting

This study will be conducted using the HIRD, which includes longitudinal medical and pharmacy claims data for about 75.5 million Anthem or Anthem-affiliated health plan members across the United States (US). For additional data regarding the HIRD, see Section 9.4 Data Source.

Tracking Uptake of Study Drugs and Feasibility Assessment

The source population for this study consists of the HIRD population with pharmacy and medical benefits, 31 January 2020 to 31 December 2027. This will allow for the characterization of women 16-44 years of age treated with lasmiditan and comparator populations.

If patient accrual within the HIRD, is not on track to include 683 pregnant women with migraine exposed to lasmiditan (minimum required to detect a prevalence ratio of 2 with a 4:1 comparator to lasmiditan ratio for MCMs analysis) by the end of 2027, additional options will be assessed, including extending the timeline for patient accrual or expanding the size of the study population by adding data partners. HealthCore has experience and is prepared to serve as the data coordinating centre in a multi-database study should this be required to achieve the desired sample size.

Comparative Analysis

Inclusion criteria:

- The study population shall consist of pregnant women with at least one pregnancy or delivery code;
- Women between the ages of 16-44;
- At minimum six months of continuous enrollment in the HIRD database prior to the estimated start of pregnancy, however, if the woman has been in the database for greater than 6 months then all available data will be used;
- For the lasmiditan exposed and comparator groups a diagnosis of migraine any time before or during pregnancy. Migraine is clinically defined as a recurrent headache disorder characterized by painful attacks lasting four to 72 hours and usually accompanied by other symptoms including nausea, vomiting, sensitivity to light and sound, and changes in vision.[14]

Exclusion criteria:

- Pregnancies with teratogen exposure as identified in claims data (Appendix 3 List of Teratogens), including but not limited to exposure to warfarin, antineoplastic agents, isotretinoin, misoprostol, lithium, thalidomide, or anticonvulsants (i.e., phenytoin, valproic acid, trimethadione, paramethadione, and carbamazepine) as well as their respective pre-pregnancy exposure period based on the teratogen's half-life (at least five half-lives prior to pregnancy for all teratogenic exposures) will be excluded from the analyses of MCMs. Identification of exposure to teratogens will be based upon prescription fills and medical encounter claims.
- Pregnancies with insufficient data to define the start of pregnancy (e.g., diagnosis or procedure indicating pregnancy without a documented outcome).

Lasmiditan Cohort patients will also be required to have:

- At least one pharmacy dispensing for lasmiditan at any time during the study period from 30 days prior to the estimated LMP anytime during the first trimester (primary objective), 30 days prior to the estimated LMP through the end of pregnancy (secondary objective), or last recorded pregnancy code (for pregnancies without documented end dates/outcomes).

- No pharmacy dispensing for other acute migraine medications (see Appendix 1 Code Lists) from 30 days prior to the estimated LMP anytime during the first trimester (primary objective), 30 days prior to the estimated LMP through the end of pregnancy (secondary objective), or last recorded pregnancy code (for pregnancies without documented end dates/outcomes).

Comparator Cohorts must meet the following:

Lasmiditan Unexposed Cohort

- No dispensing of lasmiditan at any time during the study period from 30 days prior to the estimated LMP anytime during the first trimester (primary objective), 30 days prior to the estimated LMP through the end of pregnancy (secondary objective), or last recorded pregnancy code (for pregnancies without documented end dates/outcomes).

- At least one diagnosis of migraine or a dispensing of acute migraine medication (e.g., gepants, triptans, etc.) on or before the end of pregnancy (e.g., delivery, spontaneous abortion, elective termination) or last observed pregnancy code (for pregnancies without documented end dates/outcomes).

Triptan cohort:

- No dispensing of lasmiditan at any time during the study from 30 days prior to the estimated LMP anytime during the first trimester (primary objective), 30 days prior to the estimated LMP through the end of pregnancy (secondary objective) or last recorded pregnancy code (for pregnancies without documented end dates/outcomes). At least one dispensing of triptans within 30 days prior to or during pregnancy.

- No other migraine-specific medications from 30 days prior to the estimated LMP anytime during the first trimester (primary objective), 30 days prior to estimated LMP through the end of pregnancy (secondary objective), or last recorded pregnancy code (for pregnancies without documented end dates/outcomes).

Gepants cohort:

- No dispensing of lasmiditan at any time during the study period from 30 days prior to the estimated LMP anytime during the first trimester (primary objective), 30 days prior to the estimated LMP through the end of pregnancy (secondary objective) or last recorded pregnancy code (for pregnancies without documented end dates/outcomes). At least one dispensing of gepants within 30 days prior to or during pregnancy.

- No other migraine-specific medications from 30 days prior to the estimated LMP anytime during the first trimester (primary objective), 30 days prior to the estimated LMP through the end of pregnancy (secondary objective), or last recorded pregnancy code (for pregnancies without documented end dates/outcomes).

9.3. Variables

Dates and Time Periods

The following dates and time periods will be used in this study:

- **Study period:** 31 January 2020 (start of lasmiditan market availability) to 31 December 2027
- **End of pregnancy date:** This value is determined by the date of a claim for a pregnancy outcome. See the Quality Assurance Procedures section for additional considerations regarding this approach.
- **Last Menstrual Period (LMP):** Last menstrual period will be estimated using gestational age, available from ICD-10 Z3A codes (Appendix 1 Code Lists). When Z3A codes are missing, gestational age will be imputed from ICD-10 P07.2 and P07.3 codes in premature/immature linked infants where feasible or will be assigned based on the type of delivery (e.g., premature, stillbirth, spontaneous abortion) consistent with previously published studies.[15-17]
- **Exposure assessment window:** Primary analysis for composite MCM will include women who are exposed to lasmiditan from 30 days prior to the last menstrual period through the first trimester. For secondary outcomes, this period spans from 30 days prior to the last menstrual period through the end of pregnancy date. For analyses stratified by trimester of exposure, exposure in each trimester will be assessed separately.
- **Covariate assessment period:** This is the pre-pregnancy period used to measure the covariates that will be placed into the propensity score models. This period consists of a minimum of six months of continuous enrollment prior to the estimated start of pregnancy as specified by the study inclusion criteria and will extend to all available lookback[18] when the continuous enrollment in the HIRD for any women is greater than 6 months.

Study Drugs Exposure Definition and Assessment

Exposure to study drugs will be identified using claims for prescription fills. Generic Product Identifier and/or National Drug Codes will be used to identify prescription fills. Primary analysis for composite MCM will include women who are exposed to lasmiditan from 30 days prior to the last menstrual period through the first trimester. For secondary outcomes, the exposure assessment window will span from 30 days prior to the last menstrual period through the end of the pregnancy date.

Drugs indicated for the acute treatment of migraine are taken on an as-needed basis. A patient who fills a prescription for lasmiditan may not take the drug until she has a migraine, which may not occur at the time of pharmacy dispensing. In this way, as-needed drugs differ from

preventive or maintenance medications which are supposed to be taken regularly. While exposure to medications that are meant to be taken at regular intervals can be assessed using a combination of fill dates, days' supply, grace periods, and drug half-life, exposure assessment for as-needed drugs calls for a different approach.

Chronic migraine sufferers are likely to use more medication in a shorter period of time, while episodic migraine sufferers may use less medication over a longer period of time. In claims data, it is not possible to identify migraine attack frequency and actual drug utilization. Therefore, for all acute migraine medications received via pharmacy dispensing, the period of exposure will be defined as the date of dispensing + the days' supply + 30 days from the end of the observed days' supply. Because lasmiditan, triptans, and gepants are used as needed with relatively short half-lives (see Table 1), 30 days will be used as a gap period between the end of days' supply and the next fill date in order to better capture any potential exposure during pregnancy.

Exposure will be ascertained from pharmacy claims (Appendix 1 Code Lists). In order to ascertain additional details about the timing of exposure, a validation study will be conducted using medical records as the gold standard to identify exposure and timing of acute migraine medication (lasmiditan, triptans, and gepants) and compare these data with the claims data. A total of 100 randomly selected medical records per exposure group (lasmiditan, triptans, and gepants) will be obtained and any additional information will be extracted regarding exposure (e.g., maximum monthly dosage, exposure during specific trimester). Performance characteristics of the claims data will be used to inform an analysis of bias from exposure misclassification to estimate the impact of the exposure misclassification on the effect estimates for each of the outcomes in the study. A count of 100 records per exposure group will provide sufficient information regarding the use of 'as needed' acute migraine medication; though, a pilot study will be conducted to evaluate information available from the medical records (approximately 20 of the 100 medical records per exposure group will be used for the pilot study, these will also be randomly selected). Furthermore, if medical record review does not provide sufficient information, a bias analysis with assumptions about the percent of women for whom the exposure may have been misclassified (e.g. 5%, 10%, 20%, 30% misclassified) will be conducted to estimate the impact of potential exposure misclassification on the study's estimates of effect. Additional operational details and updated code lists will be provided in the statistical analysis plan (SAP).

Sensitivity analyses will examine assumptions about exposure timing relative to the estimated start of pregnancy (Section 9.7 Data Analysis).

Table 1. Half-life by the study drug

Study Drug	Half-Life
Lasmiditan	6 hours
Sumatriptan	2 hours
Naratriptan	6 hours

Zolmitriptan	3 hours
Rizatriptan	3 hours
Almotriptan	4 hours
Frovatriptan	26 hours
Eletriptan	4 hours
Ubrogepant	6 hours
Rimegepant	11 hours
Atogepant	10 hours

Outcome Definition and Assessment

Pregnancy Outcomes

Prevalences of pregnancy, maternal and fetal/infant outcomes will be presented, along with 95% confidence intervals.

In addition to estimating births (including healthy live births), eight adverse pregnancy and infant outcomes are included with clinical definitions as follows:

1. **Major congenital malformations (composite and individual)** –anomalies that affect life expectancy, health status, or physical or social functioning.[19] For analysis of MCMs, the following will be excluded:
    a. Outcomes that are associated with prematurity (e.g., patent ductus arteriosus in an infant delivered prior to 37 weeks gestational age).
    b. Syndromic or chromosomal cause (e.g., Trisomy 13, Trisomy 18, Trisomy 21, other trisomies and monosomies, Turner's syndrome, other chromosomal anomalies, and other specified congenital malformation syndromes affecting multiple systems), based on any claim with at least one code identified at least 10 weeks after the LMP.
    c. Infants where the pregnancy was impacted by infections known to cause malformation, identified by a diagnosis code (listed below) at any time during pregnancy.
    d. Infants with prenatal exposure to teratogens, defined as a mother receiving a pharmacy dispensing or administration of the teratogen listed in Appendix 3 Teratogens.
2. **Spontaneous abortion** –pregnancy loss before the 20th week of pregnancy.[20]
3. **Stillbirth** –involuntary fetal loss greater than or equal to 20 weeks of gestation, or fetus weighing greater than or equal to 350g, as recommended by the American College of Obstetricians and Gynecologists.[21]

4. **Preterm birth** –delivery before the 37th week of pregnancy.[22]
5. **Small-for-gestational-age**–infant birth weight less than the 10th percentile for gestational age.[23]
6. **Gestational hypertension** - hypertension (blood pressure higher than 140/90 mm Hg on two separate dates) without proteinuria or severe features that develops after 20 weeks of gestation in a woman with previously normal blood pressure and blood pressure levels return to normal in the postpartum period.[24]
7. **Pre-eclampsia** –characterized by abrupt hypertension, proteinuria, hyperreflexia , and edema of the hands, feet, and face.[25,26]
8. **Eclampsia** –new onset seizures in a pregnant woman with pre-eclampsia.[27]

Instances where the outcome of a pregnancy is not documented (e.g., 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 and described; however, they will not be included in the descriptive or comparative analyses.

Each pregnancy outcome will be ascertained from claims (Appendix 1 Code Lists). Because claims algorithms for these outcomes have yet to be validated for ICD-10, algorithms used Fto identify outcomes in the claims will be validated using medical records as a gold standard. Performance characteristics will be used to inform quantitative bias analysis to assess the impact of potential misclassification on results. Supplemental medical record data will be requested for all patients. Medical record abstraction will be conducted by a third-party vendor to validate each outcome. This medical record data will be used to confirm the presence or absence of the pregnancy outcome assigned to the women based on the findings from the claims database. Based on previous experience, approximately 70% of the requested records are expected to be obtained.

Additionally, HealthCore and Eli Lilly are concurrently conducting a post-approval pregnancy study for another preventive migraine drug, galcanezumab (PMR 3498-3). The galcanezumab study includes medical record validation for MCMs in a migraine population identified in the HIRD. The study team will use the findings from the galcanezumab study as well as any published algorithms that become available to inform the best approach for identifying MCMs for the present study. Additional detail of operational definitions and updated code lists will be provided in the SAP.

Mother-Infant Linkage

Mothers and infants who are insured by the same Anthem plan share the same Subscriber identification (ID) and have a different Member/Dependent ID number (e.g., 00, 01, 02). Infants will be linked to mothers by their matching Subscriber ID and alignment of their date of birth with the mother's recorded delivery date. To be considered a match, the infant's birth date and mother's recorded delivery date must not differ by more than three days, as developed for the Sentinel Initiative.[28] On average, 70-80% of all mothers are linked to their infants in the HIRD.

Infants and mothers who are insured by separate plans cannot be linked because they will not share a Subscriber ID. This can occur when the mother and father subscribe to separate plans and the infant is enrolled on the father's plan.

Covariate Definition and Assessment

The study will use propensity-scores to control for bias due to confounding. Covariates to be considered for inclusion in the propensity score are specific to each outcome as described in Table 2. Unless otherwise specified in the list below, the covariate assessment period is the minimum six-month continuous enrollment period prior to the Exposure Assessment Window, which begins 30 days prior to the LMP. If unable to achieve sufficient sample size with this requirement, the study team will consider shortening the required baseline period, as needed.

The covariate list below includes risk factors and associated variables for the study outcomes (Appendix 1 Code Lists).[29-35]

The following maternal variables will be considered for inclusion in the propensity score models if assessed prior to exposure to a study drug (Table 2), and these covariates will be assessed during the entire covariate assessment period unless specified differently:

- Migraine type
    a. With vs. without aura
    b. Chronic vs. episodic migraine
- Migraine severity (with vs. without intractable pain)
- Use of migraine preventive drugs (e.g., galcanezumab, onabotulinumtoxinA)
- Use of other prescription acute migraine drugs (e.g., prescription non-steroidal anti-inflammatory drugs (NSAIDs))
- Demographics and biometrics:
    a. Region of residence
    b. Age at start of pregnancy
    c. Overweight and obesity
    d. Duration of health plan enrolment prior to pregnancy
    e. Calendar date of pregnancy outcome
- Healthcare Utilization (six-month baseline period):
    a. Count of office visits, emergency department visits, and hospitalizations
    b. Number of distinct medications used
    c. Specialty of study drug prescriber, as available
- Cardiovascular, metabolic, renal:
    a. Cardiovascular disease
    b. Chronic kidney disease
    c. Diabetes mellitus type 1 or 2
    d. Hyperlipidemia
    e. Hypertension
    f. Stroke or transient ischemic attack
    g. Thrombophilia (hypercoagulability, prothrombotic state)

- Mental health and interpersonal violence:
    a. Anxiety disorder
    b. Bipolar disorder
    c. Depression
    d. Domestic violence
    e. Post-traumatic stress disorder
    f. Substance abuse (including alcohol and nicotine)
- Other diseases:
    a. Anemia of any kind
    b. Cancer (any type)
    c. Intractable migraine or status migrainosus
    d. Lupus
    e. Malnutrition
    f. Sickle cell disease
    g. Thyroid disease
    h. Top 25 diagnoses and procedures
- Infectious diseases (assessed during pregnancy):
    a. Toxoplasmosis
    b. Bacterial vaginosis
    c. Syphilis
    d. Varicella-Zoster
    e. Parvovirus B19
    f. Rubella
    g. Cytomegalovirus
    h. Herpes
    i. Human Immunodeficiency Virus
    j. Urinary tract infections
    k. Upper respiratory infection
    l. Gonorrhea
    m. Chlamydia
    n. Listeriosis
    o. Zika virus
    p. COVID-19 (This has not been shown to have teratogenic potential but will be monitored)
- Gynecologic:
    a. Endometriosis or adenomyosis
    b. Menorrhagia or dysmenorrhea
    c. Urinary tract infection
    d. Uterine fibroid
- Obstetric (assessed during the baseline period unless specified):
    a. Pregnancies with chromosomal abnormalities
    b. Assisted reproductive technology for this pregnancy
    c. Gestational diabetes (assessed during pregnancy)

d. History of preterm birth or incompetent cervix
e. Intrauterine device in place during pregnancy (assessed during pregnancy)
f. Multifetal gestation (twin, triplet, etc.)[36]
g. Parity
h. Placental abruption (assessed during pregnancy)
i. Placenta previa (assessed during pregnancy)
j. Preeclampsia and eclampsia (assessed during pregnancy)
k. Prenatal visits (assessed during pregnancy)
l. Prenatal test performed (assessed during pregnancy
m. Previous small-for-gestational-age
n. Previous stillbirth
o. Prior cesarean
p. Prior miscarriage
q. Recent pregnancy (less than six months between birth and conception)[30]
r. Subchorionic hemorrhage or hematoma
s. Congenital uterine abnormalities
t. Vaginal bleeding

- Pharmaceuticals (note that teratogen exposed patients are excluded; see Section 9.2 Setting):
  a. Top 25 filled prescriptions
  b. Amphetamines
  c. Opioids
  d. Hormonal contraceptives
  e. Prescription analgesics (e.g., opioids, NSAIDs)
  f. Antidepressants
  g. Anti-epileptic medications
  h. Antipsychotics
  i. Antihypertensive medications
  j. Antiplatelet agents
  k. Anticoagulants
  l. Vaccines received from six months prior to LMP through the end of pregnancy:
     i. Influenza
     ii. Tetanus, diptheria, and acellular pertussis (Tdap)
     iii. Hepatitis A
     iv. Hepatitis B
     v. Human papillomavirus
     vi. Measles, mumps, and rubella
     vii. Meningococcal
     viii. Pneumococcal
     ix. Varicella
     x. COVID-19

Table 2. Covariates included in each analysis, by study outcome

Covariate	MCMs	SA	Stillbirth	PTB	SGA	PE	ECL	GH
Maternal Demographic & Social Characteristics	x	x	x	x	x	x	x	x
Maternal Clinical Characteristics	x	x	x	x	x	x	x	x
Maternal Medication Use	x	x	x	x	x	x	x	x
Maternal Gynecologic Characteristics	x	x	x	x	x	x	x	x
Maternal Mental Health and Interpersonal Violence	x	x	x	x	x	x	x	x
Maternal OB Characteristics	---	---	---	---	---	---	---	---
Assisted reproductive technology for this pregnancy	x	x	x	x	x	x	x	x
Multiple gestations	x	x	x	x	x	x	x	x
Multifetal gestation	x	x	x	x	x	x	x	x
Gestational diabetes	x	NI	x	x	x	x	x	x
History of preterm birth or incompetent cervix	x	x	x	x	x	x	x	x
Intrauterine device in place during pregnancy	x	x	x	x	x	x	x	x
Placental abruption	x	NI	x	x	x	NI	NI	NI
Placenta previa	x	NI	x	x	x	NI	NI	NI
Pre-labor rupture of membranes	x	NI	x	x	x	NI	NI	NI
Pre-eclampsia or Eclampsia	x	NI	x	x	x	NI	NI	NI
Number of prenatal visits	x	x	x	x	x	x	x	x
Previous small-for-gestational-age	x	x	x	x	x	x	x	x
Previous stillbirth	x	x	x	x	x	x	x	x
Prior cesarean	x	x	x	x	x	x	x	x
Prior miscarriage	x	x	x	x	x	x	x	x
Recent pregnancy (less than six months between birth and conception)	x	x	x	x	x	x	x	x
Subchorionic hemorrhage or hematoma	x	x	x	x	x	x	x	x
Congenital uterine anomalies	x	x	x	x	x	x	x	x
Vaginal Bleeding	x	x	x	x	x	x	x	x

Abbreviations: LBW, low birth weight; MCM, major congenital malformations; NI, not include; OB, obstetric; PE, pre-eclampsia; PTB, preterm birth; SA, spontaneous abortion; SGA, small-for-gestational-age.
x=include in propensity score analysis.

Missing Data

In claims data, diseases and treatments are ascertained by presence of diagnosis, procedure, or medication codes on claims. The absence of a diagnosis, procedure, or medication code is taken to mean the absence of the event. Therefore, there is no way to identify "missing" values for

presence or absence of a condition or treatment in claims. To allow for analysis, it is assumed that absence of a code or chart note regarding a diagnosis, procedure, or medication implies its absence or irrelevance to a given patient at a given time.

Missing demographic variables other than age and sex will be quantified and reported in results tables either as a row for "missing" (for categorical or discrete variables) or as a footnote (for variables reported as continuous). Patients with missing age and sex are excluded from the HIRD.

9.4. Data Source

This study will be conducted using the HIRD, which includes longitudinal medical and pharmacy claims data from Anthem or Anthem-affiliated health plan members across the US. Claims will be utilized as the data source for exposure status, endpoints, and covariates. The HIRD includes 75.5 million patients, including 56.7 million whose data are available for research studies (the "Researchable" population).

9.5. Study Size

On the date lasmiditan was commercially available (31 January 2020), the HIRD researchable population was 50% female, had a median age of 40 (interquartile range [IQR]: 25-56), and members lived in 20 different states: 38% in the South, 25% in the Midwest, 23% in the West, and 14% in the Northeast. There were 8,354,144 reproductive-aged (16-44 years) female patients with at least one claim in the HIRD as of October 1, 2015 through December 31, 2020, of whom 585,948 had a migraine diagnosis code (ICD-10 G43 code) during this period. These 585,948 women contributed a total of 2.8 million enrollment years (Median: 4.21 years, IQR: 2.16-6.77 years) during this time period. Using the time period between 2015 through 2020 demonstrates the large population of reproductive aged women with the migraine diagnosis available in the HIRD for this analysis. Since January 31, 2020 there have been 28 women between the ages of 16 and 44 who were dispensed lasmiditan during pregnancy. Additional descriptive details of the study population can be found in Appendix 4 Feasibility Assessment.

As lasmiditan penetrates the market, HealthCore will track patent accrual in the HIRD against the required study size to conduct comparative analyses (Table 3). HealthCore will estimate the time required to achieve the desired study size and whether accrual is on track to initiate comparative analyses on schedule, or whether uptake is behind schedule. If patient accrual does not appear to be on track to reach a minimum of 683 lasmiditan users by the end of 2027, options for extending the timeline for patient accrual or expanding the size of the study population by adding one or more data partners will be assessed.

Table 3 displays a range of sample sizes needed to detect prevalence ratios (PR) of 2.0 through 4.0 with 80% power given a 1:1, 2:1, 3:1, and 4:1 comparator:lasmiditan ratio for each of the study outcomes. A minimum detectable PR of 2.0 with 4:1 comparator:lasmiditan is targeted. However, if patient accrual does not allow for a 4:1 matching ratio, this will be adjusted to an appropriate matching ratio of either 3:1, 2:1, or 1:1. See Table 3 for associated sample size. The

final minimum detectable PR and matching ratio will be determined at the end of the enrollment period (2026).

It is estimated that 65% of women in the study will be placed into the unexposed comparator group,[5] 25% will be placed into the triptans or gepants group,[5] and 5% will be placed into each of the lasmiditan group, and thus the target accrual of patients is a 4:1 comparator: lasmiditan ratio seems feasible. However, given the COVID-19 pandemic we have presented target sample sizes for a number of matching ratios and will utilize whichever is feasible by the end of the enrollment period (2027) (Table 3). Additionally, this study has accounted for a 65% live birth rate (Table 3, Accounting for Birth Rate) and 75% linkage rate in the HIRD (Table 3, Account for Database Linkage) and provided target sample size for lasmiditan exposed and comparator pregnancies needed to detect a range of minimum detectable PRs (Table 3, *N Pregnancies lasmiditan: comparator*).

Background prevalence estimates were taken from the literature. Where possible, prevalence estimates are among women with migraine, women appearing in health insurance claims databases similar to the HIRD, or both. Because stillbirths, gestational hypertension, and eclampsia are relatively rare, the sample sizes required for detection of a PR of 2.0 through a PR of 4.0 are higher than for the other outcomes.

Table 3. Sample size required to detect a PR of 2.0 – PR of 4.0 [z-alpha = 1.645, power = 80%] with 1:1, 2:1, 3:1, and 4:1 comparator: lasmiditan matching ratio

Outcome	Prevalence of Outcome	Detectable Prevalence Ratio	lasmiditan: comparator	Required Users for 80% Power	Accounting for Birth Rate ^	Account for Database Linkage*
Major congenital malformations (1:4 lasmiditan to comparator)	3%[37]	4	105:418	51	78	105
		3	205:821	100	154	205
		2	683:2731	333	512	683
Major congenital malformations (1:3 lasmiditan to comparator)	3%	4	115:345	56	86	115
		3	224:671	109	168	224
		2	738:2215	360	554	738
Major congenital malformations (1:2 lasmiditan to comparator)	3%	4	133:267	65	100	133
		3	258:517	126	194	258
		2	845:1690	412	634	845
Major congenital malformations (1:1 lasmiditan to comparator)	3%	4	193:193	94	145	193
		3	365:365	178	274	365
		2	1169:1169	570	877	1169
Spontaneous abortions (1:4 lasmiditan to comparator)	11%[7]	4	23:90	11	17	23
		3	47:189	23	35	47
		2	166:665	81	125	166

Spontaneous abortions (1:3 lasmiditan to comparator)	11%	4	27:80	13	20	27
		3	53:160	26	40	53
		2	178:535	87	134	178
Spontaneous abortions (1:2 lasmiditan to comparator)	11%	4	31:62	15	23	31
		3	59:119	29	45	59
		2	203:406	99	152	203
Spontaneous abortions (1:1 lasmiditan to comparator)	11%	4	43:43	21	32	43
		3	84:84	41	63	84
		2	281:281	137	211	281
Stillbirths (1:4 lasmiditan to comparator)	1%[38]	4	324:1296	158	243	324
		3	638:2552	311	478	638
		2	2111:8443	1029	1583	2111
Stillbirths (1:3 lasmiditan to comparator)	1%	4	355:1065	173	266	355
		3	691:2074	337	518	691
		2	2275:6825	1109	1706	2275
Stillbirths (1:2 lasmiditan to comparator)	1%	4	414:829	202	311	414
		3	800:1600	390	600	800
		2	2605:5210	1270	1954	2605
Stillbirths (1:1 lasmiditan to comparator)	1%	4	601:601	293	451	601
		3	1136:1136	554	852	1136
		2	3608:3608	1759	2706	3608
Preterm births (1:4 lasmiditan to comparator)	7.5%[7]	4	37:148	18	28	37
		3	76:304	37	57	76
		2	256:1026	125	192	256
Preterm births (1:3 lasmiditan to comparator)	7.5%	4	41:123	20	31	41
		3	82:246	40	62	82
		2	277:831	135	208	277
Preterm births (1:2 lasmiditan to comparator)	7.5%	4	49:98	24	37	49
		3	94:189	46	71	94
		2	316:632	154	237	316
Preterm births (1:1 lasmiditan to comparator)	7.5%	4	70:70	34	52	70
		3	133:133	65	100	133
		2	437:437	213	328	437
Small-for-gestational-age (1:4 lasmiditan to comparator)	3.5%[39]	4	88:353	43	66	88
		3	174:697	85	131	174
		2	583:2330	284	437	583
Small-for-gestational-age (1:3 lasmiditan to comparator)	3.5%	4	94:283	46	71	94
		3	189:566	92	142	189
		2	628:1883	306	471	628
Small-for-gestational-age (1:2 lasmiditan to comparator)	3.5%	4	113:226	55	85	113
		3	219:439	107	165	219
		2	718:1436	350	538	718

Small-for-gestational-age (1:1 lasmiditan to comparator)	3.5%	4	162:162	79	122	162
		3	310:310	151	232	310
		2	993:993	484	745	993
Gestational Hypertension (1:4 lasmiditan to comparator)	1.70%[40]	4	189:755	92	142	189
		3	371:1485	181	278	371
		2	1231:4923	600	923	1231
Gestational Hypertension (1:3 lasmiditan to comparator)	1.70%	4	207:622	101	155	207
		3	402:1206	196	302	402
		2	1325:3975	646	994	1325
Gestational Hypertension (1:2 lasmiditan to comparator)	1.70%	4	240:480	117	180	240
		3	466:931	227	349	466
		2	1518:3036	740	1138	1518
Gestational Hypertension (1:1 lasmiditan to comparator)	1.70%	4	349:349	170	262	349
		3	661:661	322	495	661
		2	2101:2101	1024	1575	2101
Pre-eclampsia (1:4 lasmiditan to comparator)	4.6%[41]	4	66:263	32	49	66
		3	129:517	63	97	129
		2	437:1748	213	328	437
Pre-eclampsia (1:3 lasmiditan to comparator)	4.6%	4	72:215	35	54	72
		3	142:425	69	106	142
		2	470:1409	229	352	470
Pre-eclampsia (1:2 lasmiditan to comparator)	4.6%	4	84:168	41	63	84
		3	164:328	80	123	164
		2	537:1072	262	403	537
Pre-eclampsia (1:1 lasmiditan to comparator)	4.6%	4	121:121	59	91	121
		3	232:232	113	174	232
		2	745:745	363	558	745
Eclampsia (1:4 lasmiditan to comparator)	0.30%[41]	4	1097:4390	535	823	1097
		3	2152:8607	1049	1614	2152
		2	7099:28298	3461	5325	7099
Eclampsia (1:3 lasmiditan to comparator)	0.30%	4	1198:3594	584	898	1198
		3	2330:6991	1136	1748	2330
		2	7655:22966	3732	5742	7655
Eclampsia (1:2 lasmiditan to comparator)	0.30%	4	1401:2802	683	1051	1401
		3	2699:5399	1316	2025	2699
		2	8771:17543	4276	6578	8771
Eclampsia (1:1 lasmiditan to comparator)	0.30%	4	2029:2029	989	1522	2029
		3	3834:2834	1869	2875	3834
		2	12146:12146	5921	9109	12146

Abbreviations: PR, Prevalence ratio; N, number
Note: Calculations completed in Episheet [42]

^ Accounts for the 65% of pregnancies that result in live births. This number was calculated by (minimum required lasmiditan users/ 0.65).
*Accounts for the ~25% of infants who are not linked to their mothers in the HIRD. This number was calculated by (minimum required lasmiditan users/ 0.75).

9.6. Data Management

All data management and analyses will be conducted by HealthCore.

9.7. Data Analysis

The steps needed to produce the analytic dataset and generate study results will be described in detail in the SAP.

Statistical Methodology

Descriptive statistics will be provided for baseline characteristics, exposure, and pregnancy outcomes for the study population (sample size (N), median, mean, standard deviation, minimum, maximum, and range, where applicable, for continuous variables; N and percentage of patients within each category for discrete variables). Data will be presented overall and by trimester of exposure and any exposure within 30 days of the medication prior to LMP. Among infants, if there are >10 for each cell, organ system of MCM will be stratified and presented in descriptive tables. In the event that there are ≤10 infants with a specific organ system of MCM, the value will be presented as ≤10 in the descriptive tables due to the HIRD privacy requirements.

This study will compare lasmiditan users to three comparator groups. Propensity for treatment with lasmiditan based on covariates within six months or more prior to LMP and during pregnancy (the covariate assessment period) will be estimated using all specified covariates (see "Covariate Definition and Assessment" in Section 9.3 Variables, Table 2). The inverse of the probabilities will be used to weight the data so that covariate balance is achieved for each comparison. Distribution of these inverse probability weight estimates will be described (Appendix 2, Figure 4). Covariate balance will be assessed using absolute standardized differences with a target value of less than 0.1.[43] Additionally, inverse probability weighting estimates will be based on weights truncated at the 99th percentile to prevent the influence of extreme weights.[44]

Prevalence ratios (PRs) will be estimated using log-binomial regression models. Confidence intervals with 95% coverage probability will be generated using the robust variance ("sandwich") estimator to account for non-independence between fetuses from the same womb (i.e., multifetal pregnancies and pregnancies from the same mother).

Table Cell Sizes Less Than or Equal to Ten

Due to HIRD data privacy requirements, any table cells with counts ≤10 will be populated with '≤ 10', and corresponding table cells that allow a value of 1 to 10 to be derived from other reported cells will be left blank.

9.7.1. Additional Analyses (Bias and Sensitivity)

Age Groups

To assess the possible effect modification by age, effects estimates will be calculated for the following age groups: 16–21 years, 22–39 years, and 40–44 years.

Non-Migraine Comparator Group

To determine if there is a higher risk of study outcomes among women exposed to lasmiditan as compared to the general population of pregnant women without migraine, the risk of the primary and secondary outcomes among women exposed to lasmiditan during pregnancy or 30 days before LMP will be compared to the risk among pregnant women without a diagnosis of migraine. Non-migraine patients will be identified by the lack of a migraine diagnosis during the baseline period which is a minimum of 6 months enrollment prior to LMP but will also include all available lookback in the database if the women has been enrolled in the database for greater than 6 months.

Migraine versus Non-Migraine Comparison

To assess the possible relation between migraine and study outcomes, prevalences of the eight study outcomes between women with migraine will be compared to women without migraine in the HIRD. Pending findings from this step, bias analyses may be implemented to adjust study findings from the lasmiditan:non-migraine sensitivity analysis. Non-migraine patients will be identified by the lack of a migraine diagnosis during the baseline period which is a minimum of 6 months enrollment prior to LMP but will also include all available lookback in the database.

Refills Subgroup

To address uncertainty regarding drug utilization, all main analyses will be repeated, restricting the population to pregnant women with at least two claims for lasmiditan fills as exposed and at least two claims for the comparator medication (triptans and gepants). Only women who have two or more fills will be considered exposed for the days' supply in all of their fills plus 30 days after the last fill. Requiring a lasmiditan refill strengthens the assumption that the study drug was actually being taken by the patient.

Preventive Drug Use

To examine whether migraine preventive drug use modifies any association between lasmiditan and each of the study outcomes, the main analyses will be stratified by the use of preventive migraine drugs during pregnancy.

Exclusion of Other Migraine Drugs

Women with migraine may try many types of pharmaceutical products in their attempt to find effective relief. The first comparator group described for this study consists of pregnant migraine patients unexposed to lasmiditan. It is anticipated that more than half of these women will use other migraine drugs during pregnancy.[4,5,45] Lasmiditan users may also use additional drugs

during the study period. Understanding the mixture of drugs being used in each population will provide context for study findings.

For the exposed and comparator groups of pregnant women with migraine, the proportion of pregnant women who used a prescription migraine drug other than a study drug will be reported. Models will compare women in these restricted cohorts to assess the risk of all primary and secondary outcomes.

Residual Confounding

Residual confounding by unmeasured covariates, such as non-prescription medications, will be assessed through quantitative bias analysis. For example, non-steroidal anti-inflammatory drugs (NSAIDs) may increase the risk of some study outcomes.[4,6] Over the counter NSAID data is not available in claims data. Therefore, prescription NSAIDs are used as a proxy to address this potential bias through an analysis stratified by NSAID use in each group and by trimester of exposure.

Trimester of Exposure

Because trimester of exposure is likely an effect modifier when considering the relationship between exposure to a drug and the wellbeing of a fetus, the PR will be re-computed, stratified by estimated trimester of exposure.

For each exposure group (i.e., pregnant migraine patients exposed to lasmiditan, pregnant migraine patients not exposed to lasmiditan, pregnant migraine patients exposed to triptans and not exposed to lasmiditan, and pregnant migraine patients exposed to gepants and not exposed to lasmiditan), the distribution of timing of fills or refills will be reported by trimester. Additional details will be provided in the SAP.

Only prescription fills that occurred during pregnancy will be included in the trimester specific analyses. An additional sensitivity analysis will be conducted where fills occurring in the month prior to the estimated start of pregnancy will be considered as first-trimester exposure. For each outcome, the pattern of outcome occurrence by exposure cohort will be visually examined, as well as further stratified by the time of exposure within each exposure cohort (Appendix 2, Table Shells; Figure 1 and Figure 2).

Migraine Severity

To understand the impact of migraine severity on the primary and secondary outcomes, the primary analysis will be stratified by the presence of intractable pain. The frequency of patients at baseline with and without intractable pain will be described.

Lasmiditan Dose

To assess the possible dose effects of lasmiditan, effect estimates will be stratified by the following dosages: 50 mg, 100 mg, and 200 mg. Additionally, details regarding the dosage that is discovered during the exposure validation analysis will be tabulated (Section 9.3 Variables).

Major Congenital Malformation Analysis by Organ System

To better understand if lasmiditan exposure is associated with an increased risk of MCMs in a particular organ system, the primary analysis with organ system specific MCMs as the outcomes of interest will be conducted. Organ systems of classification include cardiovascular, genitourinary, musculoskeletal, digestive, central nervous system, clefts, respiratory, integument, eye, and ear.

Attrition Bias Analysis

In order to determine the impact of attrition bias on the number of infants with an MCMs diagnosis, the distribution of time to diagnosis among infants in the HIRD who are enrolled in the study database through the first year of life will be presented. Based on this distribution, the number of infants in the sample population who may have been diagnosed with an MCM had they not been lost to follow during their first year of life and determine how this attrition bias may have impacted the effect estimates will be imputed.

Infections During Pregnancy

In order to better understand the impact of infections during pregnancy on our outcomes of interest we will conduct our primary analysis (risk of MCM among women exposed to lasmiditan anytime during the first trimester of pregnancy compared to three unexposed comparator groups) excluding women who had evidence of infection during pregnancy. The infections of interest can be found in Section 9.3 Variables. Descriptive details regarding the number and percentage of women with infections during pregnancy and infection type are provided in Appendix 2, Table Shells.

Inverse Probability Weights Without Truncation

In order to determine the impact of truncation of inverse probability weight (IPW) estimates, we will conduct a sensitivity analysis without truncation of IPW estimates in the absence of any extreme weights.

Fixed Baseline Period

In order to ensure that all available baseline time are comparable between study cohorts a distribution of this time will be provided for the study drug and comparators. If widely varying amounts of baseline time are identified, a sensitivity analysis will be conducted that limits all women in this study to a 6-month baseline period.

Novel Coronavirus Pandemic Period

The FDA approved lasmiditan tablets for the acute treatment of migraine in October 2019. The drug subsequently underwent scheduling by the Drug Enforcement Administration and became available to patients in January 2020. In March 2020, the US health care system experienced strain due to a novel coronavirus pandemic. While few patients are likely to have accessed lasmiditan during this time, the pandemic may influence outcomes in pregnant women who could be included in the comparator groups for this study. This poses a threat to study validity if adverse pregnancy outcomes are more likely at this time due to the individual and institutional stresses of an ongoing pandemic.

To mitigate this potential threat to validity, the study team will evaluate the literature and make an informed decision around how to manage data from pregnancies that took place during the pandemic period. Additionally, analyses stratified by the time period before COVID, during COVID, and after COVID to understand the impact of the pandemic on study results will be conducted.

9.8. Quality Control

All study related procedures will be in accordance with the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology,[46] Guide on Methodological Standards in Pharmacoepidemiology,[47] FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment,[48] and FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.[49]

HealthCore's research team documents the progress and scientific and quality review of all study activities and deliverables (e.g., protocol, data management, data analysis, reports, manuscripts, etc) in a Project Log. The Project Log provides documentation of the major study tasks related to a specific study activity performed by HealthCore to develop and execute the requirements of the protocol. In addition, the Project Log documents the quality assurance measures performed for each study activity during the conduct of the study. Any change to study specifications (e.g., protocol, study database, variables in the analytic files, etc) is also described in the Project Log. This is necessary to ensure that such communications are appropriately documented, that the most up-to-date versions of relevant documents are readily identifiable, and that affected documents are tracked in the Project Log.

All programming required for study database extraction and creation of the analytic datasets from the HIRD will be performed in accordance with HealthCore Programming Standards. The HealthCore Programming Standards are a set of documents describing data extraction methods that are referenced in HealthCore Standard Operating Procedures and provide a guideline for basic, frequently used terms and definitions and respective coding information to maintain operational consistency. Data validation will occur throughout the data management and analysis process. Data quality checks include, but are not limited to, programming checks by an individual who is not the main programmer for the study, internal dataset consistency, and checks to ensure that Protocol criteria were met. If validation checks are not satisfied, then an examination of the problem will be performed on the dataset or datasets in question and the problem resolved. All data validation, quality checks, and resolution of issues identified will be documented in the Project Log.

9.9. Strengths and Limitations of the Research Methods

Claims-based Databases

The main limitations relate to uncertainties regarding the numbers of subjects available to study for new medications (threats to precision), and limitations inherent in database studies, including accuracy and specificity of codes used to identify outcomes (threats to validity). An outcome

validation will be performed in order to assess the accuracy of the algorithms used in the study (Section 9.3 Variables*; Study Outcomes and Assessment*). In particular, the uptake of a new product determines the time at which a sufficient study size for analysis will accrue in the database. It is hypothesized that six years of accrual will be sufficient, however, if, at Eli Lilly's discretion, the uptake rate is too slow and projected time until analysis too long, then we would offer to expand the study size by adding other databases.

Another important limitation is that composite endpoints such as major congenital anomalies include multiple specific endpoints, some of which may not be identified accurately in claims data. However, given that effect estimates will be calculated by organ system and as a composite measure for a comprehensive understanding of lasmiditan exposure during pregnancy on the risk of MCMs, the impact of this limitation may be minimal.

Finally, the present study defines exposure based upon pharmacy fills and refills. A pharmacy claim is not a guarantee that the patient used the drug in question, and exposure may be misclassified as a result. To mitigate this limitation, a refill sensitivity analysis outlined above and exposure validation are planned (Section 9.3 Variables).

Unmeasured Covariates

This study does not have data on over-the-counter drugs that may have an effect on pregnancy. Similarly, this study cannot account for stress, environmental exposures, and health behaviors such as exercise, caffeine consumption, and sleep habits, which each may relate to migraine and early pregnancy loss, and other pregnancy outcomes. Sleep duration, body mass index, and parity may be associated with the study outcomes and are shown to be associated with migraine treatment selection during pregnancy.[5]

To mitigate this limitation, HealthCore will carry out quantitative bias analyses to assess the potential impact on results for confounders outlined in the sensitivity analyses.

Delayed Pregnancy Inclusion Bias

"Delayed pregnancy inclusion bias" results from including only those pregnancies that survived long enough to have a claim appearing in a database as is necessitated in claims studies of drug safety during pregnancy.[50] This bias might also be conceived of as "missing pregnancies bias." For example, if lasmiditan-exposed fetuses are less likely to survive, but their existence is less likely to show up in the claims because they were miscarried early, the PRs for spontaneous abortion might be biased towards the null.[51] This remains a limitation of the study. However, the study team will monitor the literature during this study and apply any novel algorithms to quantify delayed pregnancy inclusion bias.

Re-defining Start of Pregnancy Date

Exposure classification for this study depends on the study team's ability to correctly impute the LMP using claims data. A limitation to this study is the inability to directly ascertain time of conception to assess early exposure (Appendix 1 Code Lists).

Additionally, if imputation for an outcome is more likely to be incorrect, this could result in exposure misclassification that is differential by outcome status (i.e., differential misclassification) and may result in bias. To address this potential bias, the study team has utilized algorithms supported by the literature and will conduct sensitivity analyses that change the imputation algorithms based on novel algorithms developed and supported by the literature to determine if this changes the study findings.

Channeling Bias

If older drugs, such as sumatriptan, are used as a comparator, there may be women in the HIRD who used them in prior pregnancies, not captured by this database. If a woman had a bad experience with sumatriptan while pregnant, she would likely switch to a different drug if her migraines repeat during her next pregnancy. It is assumed that if she had a good experience, she would stay on the original drug. Thus, women who have had a prior poor experience with sumatriptan, or any other drug,[52] they may use a new drug, such as lasmiditan, which can lead to important information being missed about the safety profile of the old drug, in this case, sumatriptan. This is also problematic because women who had prior poor pregnancy outcomes such as spontaneous abortion are more likely to have those outcomes again. The channeling to lasmiditan for these women [52,53] could make lasmiditan appear falsely unsafe.

An additional form of channeling bias that may occur is that patients prescribed lasmiditan or gepants may include patients who have contraindications to triptans, primarily cardiovascular disorders.[7,8] These patients may experience a higher rate of adverse pregnancy outcomes.[54-57] As a result, the channeling of patients with cardiovascular disorders to lasmiditan may cause lasmiditan to appear falsely unsafe when it is compared to triptans. Additionally, the gepants comparator analysis might provide more insight into women with cardiovascular disorders as these women are equally likely to be prescribed lasmiditan or gepants.

To mitigate these limitations, HealthCore will medically adjudicate outcomes and use that data to quantify positive predictive values and conduct simple quantitative bias analyses to assess the potential impact misclassification of the outcome and a sensitivity analysis excluding patients with cardiovascular disease.

9.10. Other Aspects

Not applicable.

10. Protection of Human Subjects

Patient Information and Consent

There is no active enrolment or active follow-up of study subjects, and no data are collected directly from individuals. HealthCore maintains Data Sharing Agreements and Business Associate Agreements with all covered entities who provide data to the HIRD. HealthCore's access, use, and disclosure of Protected Health Information (PHI) are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 Code of Federal Regulations Part 160 and Subparts A and E of Part 164]. HealthCore does not access, use, or disclose identifiable PHI unless under a specific waiver of authorization (e.g., a HIPAA Waiver of Authorization from an institutional review board (IRB)). HealthCore accesses the data in a manner that complies with federal and state laws and regulations, including those related to the privacy and security of individually identifiable health information.

Institutional Review Board (IRB)

The proposed study is designed as an analysis based on medical and pharmacy claims data from a large commercially insured population in the US. Though this study does not currently require information from medical records, if necessary HealthCore would seek oversight from an independent IRB. As the IRB is independent, HealthCore cannot control the approval or whether there are conditions for the approval. A copy of the IRB approval letter would be forwarded to Eli Lilly by HealthCore.

At no time during the conduct of this study will HealthCore provide Eli Lilly information identifying patients or providers.

11. Management and Reporting of Adverse Events/Adverse Reactions

This is a non-interventional study based on secondary data use, and therefore no individual case safety report reporting is required. The study protocol-defined adverse events (AE) include spontaneous abortion, stillbirth, MCMs (composite and individual), preterm birth, and SGA infants, gestational hypertension, preeclampsia, and eclampsia. All protocol-defined AEs collected will be summarized in the interim and final study report. No other AEs will be collected.

12. Plans for Disseminating and Communicating Study Results

This study will produce interim and final reports that will be delivered to the FDA.

Results will be disseminated via presentation at scientific conferences and/or publication in peer-reviewed journals.

13. References

1. Evans R. The Clinical Features of Migraine With and Without Aura. In. *Practical Neurology*2014.
2. Burch R, Rizzoli P, Loder E. The prevalence and impact of migraine and severe headache in the united states: figures and trends from government health studies. *Headache: the journal of head and face pain.* 2018;58(4):496-505.
3. Aukes A, Yurtsever F, Boutin A, Visser M, de Groot C. Associations Between Migraine and Adverse Pregnancy Outcomes: Systematic Review and Meta-analysis. *Obstet Gynecol Surv.* 2019;74(12).
4. Amundsen S, Nordeng H, Nezvalova-Henriksen K, Stovner LJ, Spigset O. Pharmacological treatment of migraine during pregnancy and breastfeeding. *Nat Rev Neurol.* 2015;11(4):209-219.
5. Nezvalová-Henriksen K, Spigset O, Nordeng H. Maternal characteristics and migraine pharmacotherapy during pregnancy: cross-sectional analysis of data from a large cohort study. *Cephalalgia.* 2009;29(12):1267-1276.
6. Burch R. Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review. *Headache.* 2020;60(1):200-216.
7. Tanos V, Raad EA, Berry KE, Toney ZA. Review of migraine incidence and management in obstetrics and gynaecology. *Eur J Obstet Gynecol Reprod Biol.* 2019;240:248-255.
8. Do TP, Guo S, Ashina M. Therapeutic novelties in migraine: new drugs, new hope? *J Headache Pain.* 2019;20(1):37.
9. U.S. Food & Drug Administration (FDA). FDA approves new treatment for adults with migraine. https://www.fda.gov/news-events/press-announcements/fda-approves-new-treatment-adults-migraine. Published 2019. Updated 12/23/2019. Accessed 1/29/2020.
10. Brennan T. New Migraine Drugs Approach Approval: Preventive, Acute Therapies Provide Options, Could Drive Additional Cost. CVS Health Payor Solutions. Insights/Drug Pipeline Web site. https://payorsolutions.cvshealth.com/insights/new-migraine-drugs-approach-approval. Published 2019. Updated 10/16/2019. Accessed 1/29/2020, 2020.
11. American Headache Society. Rimegepant approved by FDA for the acute treatment of migraine in adults. https://americanheadachesociety.org/news/rimegepant-acute-migraine-treatment/. Published 2020. Accessed 5/13/2020.
12. Fookes C. CGRP Inhibitors. Drugs.com. https://www.drugs.com/drug-class/cgrp-inhibitors.html. Published 2018. Updated 11/7/2018. Accessed 1/29/2020, 2020.
13. EUROCAT. EUROCAT Guide 1.4: Instruction for the registration of congenital anomalies. EUROCAT Central Registry. https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/JRC-EUROCAT-Full-Guide-1.4-version-15-Nov-2019.pdf. Published 2013. Accessed.
14. Katsarava Z, Buse DC, Manack AN, Lipton RB. Defining the differences between episodic migraine and chronic migraine. *Curr Pain Headache Rep.* 2012;16(1):86-92.
15. MacDonald SC, Cohen JM, Panchaud A, McElrath TF, Huybrechts KF, Hernandez-Diaz S. Identifying pregnancies in insurance claims data: Methods and application to retinoid teratogenic surveillance. *Pharmacoepidemiol Drug Saf.* 2019;28(9):1211-1221.
16. Margulis AV, Setoguchi S, Mittleman MA, Glynn RJ, Dormuth CR, Hernandez-Diaz S. Algorithms to estimate the beginning of pregnancy in administrative databases. *Pharmacoepidemiol Drug Saf.* 2013;22(1):16-24.
17. Butler AM, Layton JB, Li D, et al. Predictors of Low Uptake of Prenatal Tetanus Toxoid, Reduced Diphtheria Toxoid, and Acellular Pertussis Immunization in Privately Insured Women in the United States. *Obstet Gynecol.* 2017;129(4):629-637.
18. Conover MM, Sturmer T, Poole C, et al. Classifying medical histories in US Medicare beneficiaries using fixed vs all-available look-back approaches. *Pharmacoepidemiol Drug Saf.* 2018;27(7):771-780.
19. DeSilva M, Munoz FM, McMillan M, et al. Congenital anomalies: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data. *Vaccine.* 2016;34(49):6015-6026.

20. Rouse CE, Eckert LO, Babarinsa I, et al. Spontaneous abortion and ectopic pregnancy: Case definition & guidelines for data collection, analysis, and presentation of maternal immunization safety data. *Vaccine.* 2017;35(48 Pt A):6563-6574.
21. Tavares Da Silva F, Gonik B, McMillan M, et al. Stillbirth: Case definition and guidelines for data collection, analysis, and presentation of maternal immunization safety data. *Vaccine.* 2016;34(49):6057-6068.
22. Quinn JA, Munoz FM, Gonik B, et al. Preterm birth: Case definition & guidelines for data collection, analysis, and presentation of immunisation safety data. *Vaccine.* 2016;34(49):6047-6056.
23. Schlaudecker EP, Munoz FM, Bardají A, et al. Small for gestational age: Case definition & guidelines for data collection, analysis, and presentation of maternal immunisation safety data. *Vaccine.* 2017;35(48 Pt A):6518-6528.
24. Mammaro A, Carrara S, Cavaliere A, et al. Hypertensive disorders of pregnancy. *J Prenat Med.* 2009;3(1):1-5.
25. Phipps E, Prasanna D, Brima W, Jim B. Preeclampsia: Updates in Pathogenesis, Definitions, and Guidelines. *Clinical journal of the American Society of Nephrology : CJASN.* 2016;11(6):1102-1113.
26. Mol BWJ, Roberts CT, Thangaratinam S, Magee LA, de Groot CJM, Hofmeyr GJ. Pre-eclampsia. *Lancet (London, England).* 2016;387(10022):999-1011.
27. Magley M, Hinson MR. Eclampsia. In: StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC.; 2020.
28. Sentinel Operations Center. Mother-Infant Linkage: FAQ & Appendices. https://www.sentinelinitiative.org/sites/default/files/data/distributed-database/MIL_FAQs_Appendices.pdf. Published 2019. Accessed.
29. National Institutes of Health (NIH). What are the risk factors for stillbirth? https://www.nichd.nih.gov/health/topics/stillbirth/topicinfo/risk. Updated 12/1/2016. Accessed 1/31/2020, 2020.
30. National Institutes of Health (NIH). What are the risk factors for preterm labor and birth? https://www.nichd.nih.gov/health/topics/preterm/conditioninfo/who_risk. Published 2017. Updated 1/31/2017. Accessed 1/31/2020, 2020.
31. Chen X, Wen S, Sun L, Yang Q, Walker M, Krewski D. Recent oral contraceptive use and adverse birth outcomes. *European Journal of Obstetrics & Gynecology and Reproductive Biology.* 2009;144(1):40-43.
32. Stavis R. Small-for-Gestational-Age (SGA) Newborn. https://www.merckmanuals.com/home/children-s-health-issues/general-problems-in-newborns/small-for-gestational-age-sga-newborn. Published 2019. Updated Jun 2019. Accessed 1/31/2020, 2020.
33. Prager S, Micks E, Dalton V. Pregnancy loss (miscarriage): Risk factors, etiology, clinical manifestations, and diagnostic evaluation. https://www.uptodate.com/contents/pregnancy-loss-miscarriage-risk-factors-etiology-clinical-manifestations-and-diagnostic-evaluation#H3842869006. Published 2019. Updated 11/27/2019. Accessed 1/31/2020, 2020.
34. Mayo Clinic. Miscarriage. Patient Care & Health Information Web site. https://www.mayoclinic.org/diseases-conditions/pregnancy-loss-miscarriage/symptoms-causes/syc-20354298. Published 2019. Updated 7/16/2019. Accessed 1/31/2020, 2020.
35. World Health Organization (WHO). Congenital anomalies. https://www.who.int/news-room/fact-sheets/detail/congenital-anomalies. Updated 9/7/2016. Accessed 1/31/2020, 2020.
36. Olsen J, Basso O. Reproductive Epidemiology. In: Ahrens W, Pigeot I, eds. *Handbook of Epidemiology.* Berlin Heidelberg: Springer-Verlag; 2005.
37. Moorthie S, Blencowe H, Darlison M, et al. Estimating the birth prevalence and pregnancy outcomes of congenital malformations worldwide. *J Community Genet.* 2018;9(4):387-396.
38. Centers for Disease Control and Prevention (CDC). What is Stillbirth? U.S. Department of Health & Human Services (HHS). https://www.cdc.gov/ncbddd/stillbirth/facts.html. Published 2019. Updated 1/29/19. Accessed 1/30/2020, 2020.
39. Fujita K, Nagasaka M, Iwatani S, et al. Prevalence of small for gestational age (SGA) and short stature in children born SGA who qualify for growth hormone treatment at 3 years of age: Population-based study. *Pediatr Int.* 2016;58(5):372-376.

40. Laine K, Murzakanova G, Sole KB, Pay AD, Heradstveit S, Räisänen S. Prevalence and risk of pre-eclampsia and gestational hypertension in twin pregnancies: a population-based register study. *BMJ Open.* 2019;9(7):e029908.
41. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ : British Medical Journal.* 2013;347:f6564.
42. Rothman KG, S; Lash, TL. *Modern epidemiology.* Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
43. Ali M, Groenwold R, Belitser S. Reporting of covariate selection and balance assessment in propensity score analysis is suboptimal: A systematic review. *J Clin Epidemiol.* 2015;68(2):122-131.
44. Cole SR, Hernán MA. Constructing inverse probability weights for marginal structural models. *Am J Epidemiol.* 2008;168(6):656-664.
45. Harris GE, Wood M, Eberhard-Gran M, Lundqvist C, Nordeng H. Patterns and predictors of analgesic use in pregnancy: a longitudinal drug utilization study with special focus on women with migraine. *BMC Pregnancy Childbirth.* 2017;17(1):224.
46. International Society for Pharmacoepidemiology (ISPE). Guidelines for Good Pharmacoepidemiology Practices (GPP). https://www.pharmacoepi.org/resources/policies/guidelines-08027/. Published 2015. Accessed.
47. European Medicines Agency. ENCePP Guide on Methodological Standards in Pharmacoepidemiology. http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml. Published 2018. Accessed.
48. U.S. Food & Drug Administration. Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-pharmacovigilance-practices-and-pharmacoepidemiologic-assessment. Published 2005. Accessed.
49. U.S. Food & Drug Administration. Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic. Published 2013. Accessed.
50. Schnitzer ME, Blais L. Methods for the assessment of selection bias in drug safety during pregnancy studies using electronic medical data. *Pharmacol Res Perspect.* 2018;6(5):e00426.
51. Huybrechts KF, Bateman BT, Hernandez-Diaz S. Use of real-world evidence from healthcare utilization data to evaluate drug safety during pregnancy. *Pharmacoepidemiol Drug Saf.* 2019;28(7):906-922.
52. Maldonado G. Toward a clearer understanding of causal concepts in epidemiology. *Ann Epidemiol.* 2013;23(12):743-749.
53. Hernán M, Robins J. *Causal Inference: What If.* Boca Raton: Chapman & Hall/CRC; 2020.
54. Roos-Hesselink J, Baris L, Johnson M, et al. Pregnancy outcomes in women with cardiovascular disease: evolving trends over 10 years in the ESC Registry Of Pregnancy And Cardiac disease (ROPAC). *Eur Heart J.* 2019;40(47):3848-3855.
55. Adam K. Pregnancy in women with cardiovascular disease. *Methodist Debakey Cardiovasc J.* 2017;13(4).
56. Abbas AE, Lester SJ, Connolly H. Pregnancy and the cardiovascular system. *Int J Cardiol.* 2005;98(2):179-189.
57. Siu S, Sermer M, Colman JM, Alvarez N, Mercier L, Morton B. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* 2001.

Annex 1. List of Standalone Documents

Appendix 1 Code Lists

Appendix 2 Table Shells

Appendix 3 List of Teratogens

Appendix 4 Feasibility Assessment

Annex 2. Additional Information