PASS INFORMATION

Title	Retrospective Cohort Study of Pregnancy Outcomes in Women Exposed to Rimegepant During Pregnancy
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Medicinal product	Nurtec ODTTM
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Procedure number	Not applicable
Marketing authorization holder(s)	Biohaven Pharmaceuticals, Inc.
Joint PASS	No
Research question and objectives	To evaluate the safety of rimegepant use in pregnancy. The primary objective is to evaluate the risk of pregnancy and infant outcomes (i.e., major congenital malformations, spontaneous abortions, fetal deaths/stillbirths, and small-for-gestational-age births) among women with migraine exposed to rimegepant during pregnancy and in 2 rimegepant-unexposed comparator groups. Specific objectives are to describe patterns of use of rimegepant in pregnant women; to estimate the frequency of pregnancy outcomes (i.e., spontaneous abortions, fetal death/stillbirths, and elective terminations), pregnancy complications (pre-eclampsia/eclampsia), and fetal/infant outcomes [i.e., (1) major congenital malformations, (2) small-for-gestational-age births, and (3) preterm births] in women who used rimegepant and in 2 unexposed comparator groups; to estimate the adjusted relative risks for the study outcomes among women exposed to rimegepant in pregnancy compared with each of the 2 unexposed comparator groups.
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Project Title: Retrospective Cohort Study of Pregnancy Outcomes in Women Exposed to Rimegepant During Pregnancy

Protocol ID Number: BHV3000-403

Authors: Elena Rivero, MD, MPH, FISPE; Andrea Margulis, MD, ScD, FISPE
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Version: 1.0

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LIST OF ABBREVIATIONS

CGRP	calcitonin gene–related peptide
CI	confidence interval
CPT	Current Procedural Terminology
DAPI	Dynamic Assessment of Pregnancies and Infants
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ED	emergency department
EU PAS Register	European Union Electronic Register of Post-authorisation Studies
FDA	Food and Drug Administration
GP	general practitioner
HCPCS	Healthcare Common Procedure Coding System
ICD	*International Classification of Diseases*
ICD-9	*International Classification of Diseases, 9th Revision*
ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
ICD-10	*International Classification of Diseases, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
IHS	International Headache Society
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
LMP	first day of last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	major congenital malformation
NSAID	nonsteroidal anti-inflammatory drug
ODT	orally disintegrating tablet
OR	odds ratio
ORD	Optum Research Database
PASS	post-authorization safety study
PPV	positive predictive value
QC	quality control
RR	relative risk
RTI-HS	RTI Health Solutions
Rx	prescription
SARS-COV-2	severe acute respiratory syndrome coronavirus 2
SGA	small for gestational age
SOP	standard operating procedure
TORCH infections	toxoplasmosis, other (syphilis, varicella zoster, parvovirus B19), rubella, cytomegalovirus (CMV), and herpes
US	United States

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ABSTRACT

Title: Retrospective Cohort Study of Pregnancy Outcomes in Women Exposed to Rimegepant During Pregnancy

Draft version 0.3

Authors: Elena Rivero, Andrea Margulis, RTI Health Solutions

Rationale and background: Rimegepant (BHV-3000), a calcitonin gene–related peptide (CGRP) receptor antagonist developed by Biohaven Pharmaceuticals, Inc. (Biohaven), was approved by the United States (US) Food and Drug Administration (FDA) in Feb-2020 for the acute treatment of migraine with or without aura in adults and in May-2021 for the preventive treatment of episodic migraine in adults. Treatment with a CGRP receptor antagonist is thought to relieve migraine by (1) blocking CGRP-induced neurogenic vasodilation (returning dilated intracranial arteries to normal), (2) halting the cascade of CGRP-induced neurogenic inflammation (which leads to peripheral sensitization), and/or (3) inhibiting the central relay of exaggerated pain signals from the trigeminal nerve to the caudal trigeminal nucleus.

Biohaven is committed to fulfilling a postmarketing requirement by the FDA Center for Drug Evaluation and Research to conduct a pregnancy outcomes study using claims or electronic medical record data with outcome validation to assess major congenital malformations (MCMs), spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to rimegepant during pregnancy relative to an unexposed comparator population. The study will include 2 unexposed comparator groups, 1 of pregnant women with migraine and another without migraine. Additionally, other outcomes of pregnancy and maternal complications of pregnancy for which there is evidence of increased risk associated with some migraine therapies or with migraine will be included as secondary study outcomes.

Research question and objectives: The primary objective of this study is to evaluate the risk of pregnancy and infant outcomes (i.e., MCMs, spontaneous abortions, fetal deaths/stillbirths, and small-for-gestational-age births) among women with migraine exposed to rimegepant during pregnancy and in 2 rimegepant-unexposed comparator groups. Specific objectives are as follows:

- Objective 1: To describe patterns of use of rimegepant and other medications for migraine in pregnant women with migraine

- Objective 2: To estimate the frequency of pregnancy outcomes (i.e., spontaneous abortions, fetal deaths/stillbirths, elective terminations), complications of pregnancy (i.e., pre-eclampsia/eclampsia), and fetal/infant outcomes [i.e., (1) MCMs, (2) small-for-gestational-age births, and (3) preterm births] in women with migraine exposed to rimegepant during pregnancy and in 2 comparator groups of pregnant women not exposed to rimegepant

- Objective 3: To estimate the adjusted relative risks for the study outcomes among women exposed to rimegepant in pregnancy compared with the unexposed comparator groups

Study design: This is an observational, retrospective, cohort study using a single health care data source of prospectively collected secondary data. The source population will be pregnant women and their children born during the study period. The study groups will include a group of pregnant women with migraine treated with rimegepant during pregnancy and the following 2 comparator groups not exposed to rimegepant:

- A primary comparator group of pregnant women with migraine treated with other medications indicated for the acute or preventive treatment of migraine during pregnancy
- A secondary comparator group of pregnant women without migraine

Claims data will be used as the source of data for ascertaining the exposure, study outcomes, and covariates. Patterns of use of rimegepant and other medications indicated for the treatment of migraine will be described in a pre-pregnancy period of 6 months. The data obtained on the use of these medications will be used to determine the appropriate time window for ascertainment of pregnancy exposure to these medications. Characteristics of pregnant women will be described at baseline using available data prior to the start of pregnancy (estimated date of last menstrual period [LMP], i.e., first day of LMP). Women will be followed from the start through the end of pregnancy, plus a 42-day postpartum period, to determine the frequency of pregnancy outcomes, including spontaneous abortion, fetal death/stillbirth, elective termination, and pre-eclampsia/eclampsia. The follow-up period will vary according to the outcome evaluated. Infants born to pregnant women in each study group will be followed through 1 year after birth to determine the prevalence of (1) MCMs, (2) small-for-gestational-age births, and (3) preterm births.

Population: The source for the study population will consist of women who were pregnant during the study period in the selected US data source. Pregnant women will have to fulfill the following eligibility criteria:

- Had a pregnancy code or a recorded pregnancy outcome (i.e., live birth, stillbirth, spontaneous abortion, or elective termination) within the study period
- Had continuous enrollment in a health plan with medical and pharmacy benefits during the 6-month period before the estimated date of LMP through a postpartum period of 42 days.

Variables: Claims will be used as the data source for exposure status, study outcomes, and covariates, as available.

Exposure: The exposure window for rimegepant will include a 30-day period prior to the estimated date of LMP until the end of pregnancy for end-of-pregnancy and infant outcomes. During the monitoring phase, the length of the exposure period prior to the estimated date of LMP will be estimated based on the calculated median number of days between consecutive dispensings recorded within a 6-month period prior to the estimated date of LMP among all pregnant women with rimegepant dispensings (hereafter “median interval”) in order to confirm whether the 30-day period prior to LMP is adequate or requires adjustment. If an adjustment is required, for each rimegepant-exposed pregnant woman, the estimated exposure window for rimegepant will start 1 median interval (days) before the estimated date of LMP and will end at

the end of pregnancy. A pregnancy will be considered exposed to rimegepant if 1 or more pharmacy dispensings occurred within this period. For the analyses on congenital malformations, the exposure window will include the defined time before the estimated date of LMP until the end of the first trimester of pregnancy. For analyses on spontaneous abortions or elective terminations, the exposure window will start at the defined time before the estimated date of LMP and extend to the end of pregnancy for pregnancies ending in spontaneous abortion or elective termination. For pregnancies that do not end in those outcomes, the exposure window will end at 20 gestational weeks, which roughly coincides with the period of ascertainment of these outcomes (i.e., < 20 gestational weeks).

Similarly, for other medications indicated for the acute or preventive treatment of migraine, the exposure window will include a period before the estimated date of LMP that will be 30 days. This period will be evaluated annually during the monitoring phase to determine the need to adjust the 30-day exposure window to a period based on the median number of days between consecutive dispensings of each type of medication (by medication category). Additionally, information obtained through a patient survey to be conducted in a sample of women of childbearing age who are users of rimegepant or other migraine medications will be used to validate the proposed approach to estimate the time window of exposure before the estimated date of LMP. This will be a one-time survey to be conducted after approximately 2 years of availability of rimegepant for preventive treatment of migraine in the data source. This period will allow for a relatively large number of users and a well-established use of rimegepant for acute and preventive treatment.

Sensitivity analyses with varying exposure windows and subgroup analyses—by whether women received rimegepant for acute treatment only, preventive treatment only, or both acute and preventive treatment—will be conducted.

Study outcomes:

Primary pregnancy study outcomes:

- Spontaneous abortions
- Fetal deaths/stillbirths

Secondary pregnancy study outcomes

- Elective terminations
- Pre-eclampsia or eclampsia (combined), during pregnancy

Primary fetal/infant study outcomes

- Major congenital malformations
- Small for gestational age

Secondary fetal/infant study outcomes

- Preterm births

Other variables (maternal characteristics):

- Demographics, duration of health plan enrollment prior to pregnancy, calendar year of pregnancy at the estimated date of LMP, calendar year of end of pregnancy, geographic region

- Prior history of medical conditions: depression and bipolar disorder, anxiety and panic disorders, schizophrenia, epilepsy and seizures, alcohol dependence, substance abuse, cluster headache, hyperlipidemia, diabetes, hypertension, malignancy, thyroid disease, respiratory disease, liver disease, chronic kidney disease, obesity and smoking as available in medical claims, cardiovascular diseases, cluster headache

- Migraine type, with or without aura, and with or without intractable pain, as available

- Maternal obstetric history: gravidity; parity; previous spontaneous abortions, pregnancy terminations, preterm births, stillbirths, live births with MCMs; gestational diabetes; and gestational hypertension, as available

- Medications from 6 months before the estimated date of LMP and during pregnancy: medications of known teratogenic potential, antidepressants, antipsychotics, oral antidiabetics, insulin, antihypertensive medications, lipid-lowering drugs, antithyroid medications, antiplatelet agents, anticoagulants, and other medications associated with the medical conditions identified previously

- Preventive migraine drugs used in the 6 months prior to and during pregnancy: topiramate, other anti-epileptics, beta-blockers, antidepressants, and botulinum toxin

- Use of acute migraine drugs, ascertained separately (1) in the 6 months prior to pregnancy and (2) during pregnancy: triptans, ergotamine derivatives, prescription nonsteroidal anti-inflammatory drugs (NSAIDs), opioids

- Health care utilization, ascertained within the 6-month period prior to the beginning of the pregnancy: office visits, telemedicine encounters, emergency department visits, hospitalizations

- Current pregnancy: multiple pregnancy, gestational diabetes, TORCH infections (toxoplasmosis, syphilis, varicella zoster, parvovirus B19, rubella, cytomegalovirus, and herpes), and SARS-COV-2 infection during pregnancy

Data sources: The patients included in this study will be drawn from the Optum Research Database (ORD), a proprietary research database that contains the eligibility data, medical claims, and pharmacy claims from a large, commercial health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US and comprise approximately 3% to 4% of the US population. This study will employ the Optum Dynamic Assessment of Pregnancies and Infants (Optum DAPI), a proprietary process that includes a set

of capabilities and established algorithms that is applied to claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link mother and infant data in an ongoing manner within the ORD. Optum DAPI links health data between women and their infants through a family identifier and by matching the dates of delivery and the infant's birth. Optum can (with appropriate approvals) access medical records for a subset of mothers or infants to ascertain covariate information, to confirm outcomes and, if needed, validate algorithms for outcome ascertainment.

Study size: The target size for this study is estimated at approximately 1,152 rimegepant-exposed pregnancies and 3,465 unexposed pregnancies in each of the 2 comparator groups. For the primary outcome MCMs, with a prevalence of 3% in unexposed pregnancies, a study size of 464 exposed pregnancies with linked infants (and 1,392 in each comparator group) would provide 80% power to reject the null hypothesis if the true population relative risk were 2. To attain this number, the percentage of pregnancies ending in live births (assumed to be 62%) and the percentage of these pregnancies that are linkable to infant records (assumed to be 65%) were considered. Previous experience indicates that over 80% of pregnancies may result in live births, and over 85% of those can be linked to infant records.

Data analysis: For Objective 1, an analysis of the use of rimegepant and other medications indicated for treatment of migraine will be conducted annually, including the number of users, and mean, standard deviation, median, interquartile range of the number of dispensings, and the number of days between consecutive dispensings for each medication (by medication category). Results will be reported for each study group in the annual interim reports.

For Objective 2, a description of the cohort attrition by eligibility criteria, selected characteristics of the pregnancies in each study group, and frequency of the study outcomes, will be reported for each study group in the annual interim reports.

For Objective 3, the safety comparative analyses. If feasible, the study groups will be matched on propensity scores to control for confounding and channeling effect. Each woman in the rimegepant-exposed group will be matched in a 1:*n* variable-matching ratio with up to 3 women in each of the comparator groups (separately).

Comparative analyses for the primary and secondary outcomes will be conducted in the propensity score–matched groups for the final study analyses when target study size has been attained, and results will be reported in the final study report. Regression models will be used to compare pregnant women with migraine exposed to rimegepant during the exposure window with women in the primary comparator group and in the secondary comparator group. Point estimates and 95% confidence intervals from crude analyses within the matched study groups will be presented. The number of pregnancies will be considered when determining which analyses can be conducted. The ability to match on propensity score is contingent on the available study size. Alternatively, a weighting method on the propensity score can be applied using inverse probability of treatment weights, or the propensity score can be applied as a covariate in multivariate regression models or as a stratification variable.

Milestones:

*Milestones: Approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies.

Start of study observation period: The study start date is the date when rimegepant is first available in the participating US data source. Rimegepant was approved by the FDA on 27-Feb-2020. The planned start of the study observation period is 16-Mar-2020, coinciding with the availability of rimegepant in the US.

End of study observation: The end of study observation is the date when the final data point has been collected from the data source following fulfillment of the target study size, expected in 2027.

AMENDMENTS AND UPDATES

None to date. This is Final Protocol Version 1.0

1 MILESTONES AND TIMELINE

The study milestones are summarized in Table 1. Start of study observation period: The study start date is the date when rimegepant is first available in the participating US data source. Rimegepant was approved by the FDA on 27-Feb-2020. The planned start of the study observation period is 16-Mar-2020, coinciding with the availability of rimegepant in the US.

End of study observation: The end of study observation is the date when the final data point has been collected from the data source following fulfillment of the target study size, expected in 2027 (Figure 1). Annual study interim reports will be submitted to the FDA starting in Apr-2022. The number of pregnancies exposed to rimegepant and the number in the unexposed comparator groups, selected characteristics of the pregnancies, and frequency of the study outcomes in each study group will be reported annually during the study observation period to inform the study size, estimate the predicted study power, inform the feasibility of obtaining the target study size, and provide an estimate of when the target study size will be reached. The final study report will be submitted to the FDA within 1 year of the study completion, expected by Apr-2029, or earlier if the target study size is reached earlier.

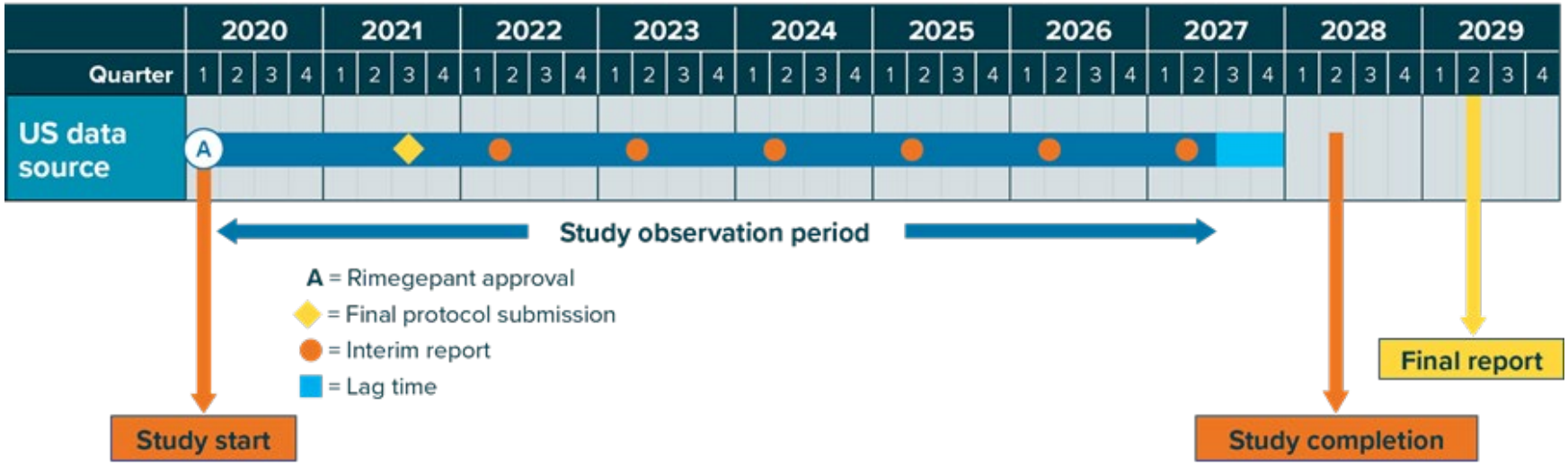
Note: Upon approval, the study will be registered in ClinicalTrials.gov and then in the EU PAS Register (European Union Electronic Register of Post-authorisation Studies).

Table 1. Study Milestones

Milestone	Planned/Actual Date
Draft protocol submission to FDA	22-Sep-2020
Final protocol submission to FDA[a]	Dec-2021
Start of study observation	16-Mar-2020
Start of data collection[b]	Q4 2021
Annual interim report to FDA	Starting in Apr-2022
End of study observation	Jun-2027
Study completion[c]	Apr-2028
Final study report	Within 1 year of availability of the final analytical data set

FDA = Food and Drug Administration.
Note: Approvals by data protection, data custodian, ethics, and scientific review bodies are pending. Timelines may be impacted by approvals of these bodies. The timeline for the final comparative analyses may be advanced if interim reports indicate that the target study size (Section 9.5) can be attained earlier; the timeline for submission of the final study report to the FDA will be modified accordingly.
[a] The date of protocol approval by FDA will drive the timing of subsequent study milestones.
[b] Start of data collection for secondary data use is "the date from which data extraction starts."
[c] Date from which the final analytical data set is available (end of data collection).

Figure 1. Study Milestone Overview



US = United States.

2 RATIONALE AND BACKGROUND

2.1 Migraine

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. It is characterized by moderate-to-severe episodic unilateral pulsating headaches that last for 4 to 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 [1].

Migraine is the seventh-highest specific cause of disability worldwide [2-4]. About 63% of migraineurs experience 1 to 4 migraines per month [5]. Migraine is more prevalent in women than in men, particularly during reproductive years [6]. The prevalence in males and females in the US adult population was 9.7% (95% confidence interval [CI], 9.1%-10.4%) and 20.7% (95% CI, 19.8%-21.6%), respectively [7]. The prevalence of migraine in women of childbearing age was 20.6% in age group 18-29 years, 28.4% in age group 30-39 years, and 25.8% in age group 40-49 years [8]. The frequency of migraines may decrease during pregnancy, particularly in the second and third trimester, and increase again after delivery [9]. The cumulative prevalence of migraine during the whole pregnancy was around 20% in 4 studies, including more than 34,000 patients [10]. However, some studies pointed out that about 40% of patients with any migraine experienced headache deterioration in early pregnancy [11].

Chronic migraine is described by the International Headache Society (IHS) as a headache that occurs on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has the features of migraine headache [1]. The prevalence of chronic migraine has been estimated to range from 1.4% to 2.2% [12].

2.2 Rimegepant and Other Treatments for Migraine

Nurtec™ orally disintegrating tablet (ODT) (rimegepant, previously known as BHV-3000), a CGRP receptor antagonist developed by Biohaven Pharmaceuticals, Inc. (Biohaven), was approved by the US FDA in Feb-2020 for the acute treatment of migraine with or without aura in adults. In May-2021, rimegepant was also approved for the preventive treatment of episodic migraine in adults. Calcitonin gene–related peptide is an endogenous 37–amino acid peptide contained within pain signaling nociceptive afferents that is thought to play a causal role in migraine [13,14]. Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: (1) serum levels of CGRP are elevated during migraine [15], (2) treatment with antimigraine medication returns CGRP levels to normal coincident with pain relief [16], and (3) intravenous CGRP infusion produces lasting pain in nonmigraineurs and migraineurs [14,17].

Treatment with a CGRP receptor antagonist is thought to relieve migraine by (1) blocking CGRP-induced neurogenic vasodilation (returning dilated intracranial arteries to normal), (2) halting the cascade of CGRP-induced neurogenic inflammation (which leads to peripheral sensitization), and/or (3) inhibiting the central relay of exaggerated pain signals from the trigeminal nerve to the caudal trigeminal nucleus [18].

As of 03-Sep-2020, more than 7,200 subjects have participated in rimegepant clinical studies. Among these subjects, more than 3,800 subjects with migraine have received a single dose of either 75 mg rimegepant or placebo in Phase 2b/3 studies. In the pivotal prevention study, a total of 527 subjects received rimegepant (every other day or every other day plus as needed up to once daily) for at least 6 months, and 311 subjects received rimegepant for at least 1 year. Collectively, the current data demonstrate a favorable benefit-risk profile for rimegepant in the acute and preventive treatment of migraine [19].

Other pharmacological treatments for the acute treatment of migraine include NSAIDs, acetaminophen, triptans, ergots, and opioids. Triptans are commonly used in migraineurs who have no relief of symptoms with NSAIDs or acetaminophen [20]. Triptans specifically bind 5-HT1B/D receptors, having vasoconstrictive effects due to their mechanism of action on serotonin (5-HT)1B receptors on the smooth muscle cells of blood vessels, and they therefore are contraindicated in patients with cardiovascular risks [20]. Up to now, 7 triptans have been approved by the US FDA for acute treatment of migraine: sumatriptan, eletriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, and almotriptan [20]. Ergots, such as ergotamine and dihydroergotamine, have been mostly replaced by triptans. Opioids are occasionally used to treat migraine [21].

Other preventive treatments for migraine in the US include tricyclic antidepressants (amitriptyline and nortriptyline), selective serotonin reuptake inhibitors (citalopram, sertraline, fluoxetine, and paroxetine), serotonin-norepinephrine reuptake inhibitor (venlafaxine), beta-blockers (propranolol, metoprolol, nadolol, and atenolol), anticonvulsant medications (gabapentin, topiramate, and divalproex) [22], and botulinum toxin. Calcitonin gene–related peptide therapy monoclonal antibodies that have been approved recently for the prophylaxis of migraine include erenumab, fremanezumab, galcanezumab [23], and eptinezumab. Persistence with migraine preventive therapy seems to be low, and switching medications or re-start after treatment discontinuation is common [24,25]. Many patients also use acute treatments while on preventive treatment [25].

2.3 Migraine and Pregnancy Outcomes

Pregnant women experiencing migraine appear to be at higher risk compared with nonmigraineurs for some complications, including gestational hypertension, pre-eclampsia, small-for-gestational-age birth, low birth weight, preterm birth, and spontaneous abortion [10].

The risk of pre-eclampsia during pregnancy was higher in women with migraine compared with nonmigraineurs in a meta-analysis, including 9 studies and about 74,000 women (adjusted pooled odds ratio [OR], 1.94; 95% CI, 1.37-2.76) [26].

The evidence for the risk of small-for-gestational-age births among pregnant women with migraine is not clear. In one cohort study, the percentage of small-for-gestational-age births was only slightly higher for migraineurs (17.7%) than among nonmigraineurs (16.8%) [27], although these results are not confirmed in a prospective study of 376 pregnant women suffering from migraine or tension headache and 326 nonheadache pregnant women [28]. In a meta-analysis of 2 studies, the adjusted pooled OR for small-for-gestational-age births was 1.06 (95% CI, 0.99-1.14) [26]. In a literature review of observational studies, the incidence of low birth weight in

pregnant women with migraine (range: 6.8%-18.7%) was higher compared with pregnant women without migraine (range: 3.6%-8%) [10]. Results from a meta-analysis, including 3 studies and more than 68,000 pregnant women suggested an increased risk of low birth weight in migraineurs compared with nonmigraineurs (adjusted pooled OR, 1.27; 95% CI, 0.89-1.82) [26].

Five studies have reported the risk of preterm birth in pregnant women with migraine. The prevalence of preterm birth was higher in pregnant women with migraine (range: 7.1%-28%) versus nonmigraine (range: 2.8%-11.4%) [10]. Results from a meta-analysis, including 2 studies published between 2008 and 2010 suggested an increased risk of preterm birth in pregnant women with migraine compared with nonmigraineurs (adjusted pooled OR, 1.25; 95% CI, 1.13-1.38) [26].

The risk of miscarriage in pregnant women have been investigated in a recent study conducted in the Danish National Registries [29]. The prevalence of miscarriage among pregnant women with migraine was 11.3% and among pregnant women without migraine was 10.3%, resulting in a prevalence ratio of 1.10 (95% CI, 1.05-1.15).

2.4 Exposure to Other Treatments for Migraine and Pregnancy Outcomes

The safety profiles of acute treatments for migraine other than rimegepant during pregnancy are diverse. Acetaminophen is usually recommended as the first option for pregnant and breastfeeding women due to its safety profile [30], although some studies reported an increased risk of pre-eclampsia and thromboembolic diseases with acetaminophen exposure during pregnancy [31]. Ergotamine and dihydroergotamine have been associated with adverse pregnancy outcomes, such as low birth weight or preterm birth [32,33].

The evidence regarding the safety of triptans is scarce, although they have been used since the early 2000s [34]. Most of the evidence comes from pregnancy registries, although more recently, some studies have been conducted in electronic health care databases. In this study, the authors compared the results from a completed, 16-year, international, prospective pregnancy registry (the sumatriptan, naratriptan, and sumatriptan/naproxen pregnancy registry between Jan 1996 and Sep 2012) [35] with a retrospective analysis conducted in the Truven Health MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases for the period of 1996 to 2012 [36]. In both studies, the majority of pregnant women were treated with triptans during the first trimester of pregnancy. The risk of major birth defects for sumatriptan exposure during the first trimester was 4% in both the claims analysis and pregnancy registry. For naratriptan and sumatriptan/naproxen sodium, the risk of major birth defects for exposure during the first trimester was 0% and 3.6% in the claims analysis and 2.2% and 0% in the registry, respectively. The risk of spontaneous abortions in women exposed to sumatriptan, naratriptan, and sumatriptan/naproxen sodium during the first trimester was 18%, 17.4%, and 18.9% in the claims analysis and 6.6%, 9.6%, and 20% in the registry, respectively. Finally, the risk of major birth defects in women exposed to sumatriptan, naratriptan, and sumatriptan/naproxen sodium during the second and third trimesters was 3.9%, 14.3%, and 7.1% in the claims analysis and 3.1%, 0%, and 0% in the registry, respectively. In a meta-analysis comparing risk of some pregnancy outcomes between pregnant women with migraine treated with triptans versus women with migraine not treated with triptans, the authors did not find an

increased risk of congenital malformations (pooled OR, 0.84; 95% CI, 0.61-1.16), spontaneous abortions (pooled OR, 1.27; 95% CI, 0.58-2.79), or preterm birth (pooled OR, 0.90; 95% CI, 0.35-2.30); when compared with healthy women, there were no increased rates of MCMs (OR, 1.18; 95% CI, 0.97-1.44) or premature births (OR, 1.16; 95% CI, 0.67-1.99); however, there was a significant increase in the rates of spontaneous abortions (OR, 3.54; 95% CI, 2.24-5.59). When the migraine no-triptan group was compared with healthy controls, a significant increase in the rates of MCMs was found (OR, 1.41; 95% CI, 1.11-1.80) [37]. A recent prospective observational cohort study conducted in Germany reported no increased risk of pregnancy outcomes or birth defects in pregnant women exposed to triptans compared with pregnant women with migraine untreated or pregnant women without migraine [38]. There was no evidence of an increased risk of major malformations, low birth weight, or prematurity associated with triptans in another systematic review and meta-analysis of medications used for the treatment of migraine [39].

A Danish population-based study found an increased risk of pregnancy-associated hypertension, miscarriage, and preterm birth and no increased risk of birth defects and small-for-gestational-age births associated with migraine. Among women who took migraine treatment (either acute, preventive, or both) compared with pregnant women who were not treated, no increased risk for miscarriage, pregnancy-associated hypertension, adverse birth outcomes including congenital malformations, or adverse neonatal or neurological outcomes in offspring was found [29]. Medications used to prevent or treat attacks of primary headache (migraine, tension headache, cluster headache, and other trigeminal autonomic cephalalgias) in women who were pregnant (or who were attempting to become pregnant), postpartum, or breastfeeding have been evaluated in a systematic literature review. The authors found that preventive treatments of migraine, including anti-epileptics (except lamotrigine), venlafaxine, tricyclic antidepressants, benzodiazepines, beta-blockers, prednisolone, and oral magnesium, may be associated with increased risk of fetal/infant adverse effects, but calcium channel blockers and antihistamines may have low risk of adverse effects [40]. Among anti-epileptics, valproic acid is teratogenic and contraindicated in pregnancy, and topiramate has been associated with oral clefts at birth [41-43].

2.5 Rationale

Biohaven Pharmaceuticals, Inc. (Biohaven) is committed to fulfilling a postmarketing requirement by the FDA Center for Drug Evaluation and Research to conduct a pregnancy outcomes study using claims or electronic medical record data with outcome validation to assess MCMs, spontaneous abortions, stillbirths, and small-for-gestational-age births in women exposed to rimegepant during pregnancy relative to an unexposed comparator population. The study will include 2 rimegepant-unexposed comparator groups of pregnant women, one with migraine and another without migraine. Additionally, other outcomes of pregnancy and maternal complications of pregnancy for which there is evidence of increased risk associated with some migraine therapies or with migraine will be included as secondary study outcomes and evaluated in women exposed to rimegepant during pregnancy compared with the unexposed comparator groups. Information on rimegepant and other common treatments for migraine in the US is summarized in Table 2.

Table 2. Information about the Use of Rimegepant in the United States

Topic	Detailed Information
Common physician specialties that diagnose migraine	Neurology
Common prescriber types for migraine (e.g., specific specialists or GPs)	Neurologists, GPs, psychiatrists
List of other common treatments for migraine	• Acetaminophen, NSAIDs, triptans (sumatriptan, eletriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, and almotriptan), ditans (lasmiditan), ergots (ergotamine and dihydroergotamine), and opioids[a] • Calcitonin gene–related peptide receptor antagonists (ubrogepant and rimegepant)[a] • Calcitonin gene–related peptide monoclonal antibodies (erenumab, fremanezumab, eptinezumab, and galcanezumab)[b] • Beta-blockers (propranolol, timolol, bisoprolol, metoprolol, atenolol, and nadolol)[b] • Anti-epileptics (gabapentin, topiramate, valproate, divalproex)[b] • Antidepressants (amitriptyline, fluoxetine, venlafaxine)[b] • Botulinum toxin (onabotulinumtoxinA)[b]
Position of rimegepant among all treatments for acute treatment of migraine	First-line treatment[c]
Approved indications and dosages for rimegepant	Rimegepant is approved for the acute treatment of migraine with or without aura in adults. The recommended dose is 75 mg taken orally, as needed. Rimegepant is also approved for the preventive treatment of episodic migraine in adults. The recommended dose is 75 mg taken orally every other day. The maximum dose in a 24-hour period is 75 mg.

GP = general practitioner; NSAIDs = nonsteroidal anti-inflammatory drugs.
[a] Acute treatment of migraine.
[b] Preventive treatment of migraine.
[c] Approved as first-line treatment. It is included in some formularies as second-line treatment.

3 RESEARCH QUESTION AND OBJECTIVES

The primary objective of this study is to evaluate the risk of pregnancy and infant outcomes (i.e., MCMs, spontaneous abortions, fetal deaths/stillbirths, and small-for-gestational-age births) among women with migraine exposed to rimegepant during pregnancy and in 2 rimegepant-unexposed comparator groups. Specific objectives are as follows:

- Objective 1: To describe patterns of use of rimegepant and other medications for migraine in pregnant women with migraine
- Objective 2: To estimate the frequency of pregnancy outcomes (i.e., spontaneous abortions, fetal deaths/stillbirths, and elective terminations), complications of pregnancy (i.e., pre-eclampsia/eclampsia), and fetal/infant outcomes [i.e., (1) MCMs, (2) small-for-gestational-age births, and (3) preterm births] in women with migraine exposed to rimegepant during pregnancy and in the following 2 comparator groups of pregnant women not exposed to rimegepant
    - Pregnant women with migraine exposed to other medications indicated for the treatment of migraine during pregnancy (primary comparator group)
    - Pregnant women without migraine (secondary comparator group)
- Objective 3: To estimate the adjusted relative risks for the study outcomes among women exposed to rimegepant during pregnancy compared with the unexposed comparator groups.

4 RESEARCH METHODS

4.1 Study Design

This is an observational, retrospective, cohort study using a single health care data source of prospectively collected secondary data. The source population will be pregnant women and their children born during the study period.

The study will include the following study groups:

- A group of pregnant women with migraine treated with rimegepant during pregnancy
- A primary comparator group of rimegepant-unexposed pregnant women with migraine treated with other medications indicated for the acute or preventive treatment of migraine
- A secondary comparator group of rimegepant-unexposed pregnant women without migraine

The primary outcomes are the following:

- Pregnancy outcomes (spontaneous abortions, fetal deaths/stillbirths);

- Fetal/infant outcomes (MCM and small-for-gestational-age births).

The secondary outcomes are the following:

- Additional pregnancy outcomes (elective terminations)
- Maternal complications of pregnancy (pre-eclampsia/eclampsia)
- Preterm births

Outcomes will be validated in the data source in the subset of cases for which researchers have access to medical records. If feasible, if target study size is attained, propensity scores will be used to control confounding in the comparative analysis.

This study will have a drug utilization component to address the first objective and a drug safety component to address the second and third objectives. The first and second objectives are part of the monitoring phase, and the third represents comparative analyses for the final study report.

The study groups of pregnant women with migraine who are treated with rimegepant, pregnant women with migraine treated with other medications indicated for migraine, and pregnant women without migraine will be identified using data from medical and pharmacy claims. Treatments other than rimegepant that are indicated for the treatment of migraine include NSAIDs, acetaminophen, triptans, ergots, opioids, beta-blockers, anti-epileptics, antidepressants, and botulinum toxin (Annex 3, Table 11).

Claims data will be used as the source of data for ascertaining the exposure, study outcomes, and covariates. Patterns of use of rimegepant and other medications indicated for the treatment of migraine will be described in a pre-pregnancy period of 6 months. The data obtained on the use of these medications will be used to determine the appropriate time window for ascertainment of pregnancy exposure to these medications (see in Section 4.3.1). Characteristics of pregnant women will be described at baseline using available data prior to the start of pregnancy (estimated date of LMP) and during pregnancy (see in Section 4.3.3). Women will be followed from the start through the end of pregnancy plus a 42-day postpartum period to determine the frequency of pregnancy outcomes, including spontaneous abortions, fetal deaths/stillbirths, elective terminations, and pre-eclampsia/eclampsia. The follow-up period will vary according to the outcome evaluated. Infants born to pregnant women in each study group will be followed through 1 year after birth to determine the prevalence of (1) MCMs, (2) small-for-gestational-age births, and (3) preterm births.

4.2 Setting

This study will be conducted in a US health care claims data source.

4.2.1 Population

The source for the study population will consist of women who have been pregnant during the study period in the selected US data source. Pregnant women will have to fulfill the following eligibility criteria:

- Had a pregnancy code or a recorded pregnancy outcome (i.e., live birth, stillbirth, spontaneous abortion, or elective termination) within the study period
- Had continuous enrollment in a health care plan with medical and pharmacy benefits during the 6-month period before the estimated date of LMP through a postpartum period of 42 days.

In this population of pregnant women, we aim to identify 3 study groups:

- Pregnant women with migraine treated with rimegepant
- Pregnant women with migraine, unexposed to rimegepant, treated with other migraine medications
- Pregnant women without migraine, unexposed to rimegepant.

4.2.1.1 Identification of Pregnancies

Potential pregnancies will be identified from women who have at least 1 medical claim with a pregnancy-related *International Classification of Diseases, 10th Revision* (ICD-10) diagnosis or procedure code, Current Procedural Terminology (CPT) code, or Healthcare Common Procedure Coding System (HCPCS) code. Diagnosis codes include those related to pregnancy, childbirth, and the puerperium (O00-O9A); weeks of gestation (Z3A); outcome of delivery (Z37); encounters for antenatal screening of the mother (Z36); supervision of normal/high risk pregnancy (Z34/O09); and maternal postpartum care (Z39). Codes for pregnancy-related procedures include those performed on the products of conception (10, 3E0E, 4A0H, 4A0J, 4A1H, 4A1J). A pregnancy episode is defined as the duration of time from the estimated LMP date (pregnancy start date) through pregnancy outcome date (pregnancy end date) [44].

The algorithm to identify pregnancy episodes uses all available codes indicating weeks of gestation (Z3A.00 to Z3A.42, excluding Z3A.49). The nonspecific Z3A codes (Z3A.00, weeks of gestation of pregnancy not specified and Z3A.01, < 8 weeks gestation of pregnancy) are included in order to identify pregnancy episodes that have only one or both codes, as these codes may be the only ones present for pregnancies ending in a loss or termination. The code Z3A.49 (> 42 weeks gestation of pregnancy) is excluded because only a very small number of women have this code. For each woman, and for each observed Z3A code (starting with the earliest claim date), the algorithm subtracts the weeks of gestation indicated by the Z3A code from the date of service indicated in the claim to estimate the LMP date. These LMP date estimations are repeated for each available Z3A code until the last claim date associated with a Z3A code is reached, resulting in multiple estimated LMP dates for each woman. Because Z3A.00 codes were

observed at various weeks of gestation among pregnancies with specific and nonspecific Z3A codes and an estimated LMP date (see below for a discussion of LMP date estimation), this code was not incorporated into the algorithm. On the other hand, Z3A.01 was mainly observed at Weeks 5-9 of gestation and was assigned 7 weeks gestation.

Several data cleaning steps are incorporated into the algorithm, for example, to remove duplicate claim lines and sequentially sort each woman's estimated LMP dates. Then, to identify and separate pregnancy episodes, the algorithm creates LMP clusters by grouping together all estimated LMP dates within 6 weeks of each other (starting with the earliest estimated LMP date and going forward to set up a 6-week window). The 6-week window was chosen based on the minimum number of weeks required between pregnancies from previous publications [44,45]. The final data cleaning steps remove the nonspecific Z3A codes (and associated LMP date estimates) if specific Z3A codes are present within a cluster. In the last step of the algorithm, the LMP date for each pregnancy episode is estimated by using the median date within each LMP cluster.

A small fraction of pregnancies do not have Z3A codes; in these cases, Optum employs an outcomes-based algorithm that estimates the LMP date by counting back the number of weeks from the occurrence of a pregnancy outcome, with varying lengths of gestation assigned for different pregnancy outcomes [45].

Based on the estimated LMP date, trimesters are defined as follows: first trimester, less than 14 weeks 0 days; second trimester, 14 weeks 0 days through 27 weeks 6 days; and third trimester, 28 weeks 0 days through delivery.

4.2.1.2 Ascertainment of Migraine

Many strategies have been used to identify migraine from electronic health data, with prevalence in pregnant women or in the general population ranging from 1% to 30% (Table 3). Of note, some studies intended to identify subjects with migraine and others intended to identify subsets of migraineurs, such as those treated with preventive medications. One study validated an algorithm with good results (sensitivity, 78%; specificity, 73%), but the target population was patients with undiagnosed chronic migraine among patients with a claim for migraine but no claims for chronic migraine [46].

One reason the ascertainment of migraine is challenging is that the diagnosis seems to be under-recorded in claims data. One study identified persons with migraine using a questionnaire with 85% sensitivity and 97% specificity and then exploring their claims patterns in a US health care system [47]. Of the questionnaire-identified subjects with migraine, 60% did not have claims for migraine or headache in the 24 months before the interview and about 25% had not filed a claim for medications commonly used to treat migraine [47].

Table 3. Algorithms for Identification of Migraine in Health Care Data, by Publication Year

Author (year)	Algorithm	Comments
Chen, Chen [27]	Using Taiwanese national data sets, the authors identified pregnant migraineurs as follows: "Of these women, 16 042 had visited ambulatory care centres for treatment of migraines (ICD-9-CM code 346) within 2 years prior to index delivery. We selected only patients who had at least 3 consensus migraine diagnoses … Ultimately, 4,911 women with migraines were included in the study cohort."	Prevalence was about 1% among pregnant women who had a singleton. Not validated.
Hepp, Dodick [24]	To identify patients with chronic migraine in MarketScan, the authors required at least 1 claim with a 346.7 ICD-9-CM code (chronic migraine) and at least 1 prescription for preventive treatment. Excluded were patients who started an antidepressant and had a claim for depression in the previous year; same for epilepsy/antiepileptic drugs and heart failure/beta-blockers.	Prevalence of chronic migraine was 0.06% Not validated.
Woolley, Bonafede [25]	Using MarketScan, the authors identified persons with migraine who were receiving preventive treatment as those with dispensings for a migraine preventive medication (topiramate, beta-blocker, or tricyclic antidepressant) and a migraine diagnosis (ICD-9-CM 346.xx) in the 12 months before the first prescription.	Prevalence of migraine cannot be assessed from the results. Not validated.
Yusuf, Chia [36]	Using MarketScan, the authors identified women with migraine as those who met at least 1 of the following criteria: "One medical claim with a migraine diagnosis (ICD-9 346.xx, in any position) associated with an inpatient stay; or "One medical claim with a migraine diagnosis (ICD-9 346.xx, in any position) associated with a neurologist visit; or "Two medical claims with a migraine diagnosis (ICD-9 346.xx, in any position) associated with an outpatient physician or ED visit 7-180 days apart; or "One medical claim with a migraine diagnosis (ICD-9 346.xx, in any position) associated with an outpatient physician visit or ED visit AND one claim for a dispensing/administration of a migraine-specific acute treatment 7-180 days apart; or "Two claims for a dispensing/administration of a migraine-specific acute treatment 7-180 days apart"	Prevalence of migraine cannot be ascertained; the authors report 1,750,000 women 10-55 years old with migraine in MarketScan This algorithm is similar to the one by Hoffman, Xue [22], described in the next row. Not validated.

Author (year)	Algorithm	Comments
Hoffman, Xue [22]	Criteria applied hierarchically in Optum data: 1a. One or more inpatient claims for migraine and one or more outpatient or ED claim for migraine, 7-180 days apart 1b. One or more inpatient claims for migraine and one or more dispensings for acute migraine-specific treatments, 7-180 days apart (1a and 1b identified 1,500 patients) 2. Two or more outpatient or ED claims for migraine, 7-180 days apart (22,500 patients) 3. One or more outpatient or ED claims for migraine and one or more dispensings for acute migraine-specific treatments, 7-180 days apart (15,300 patients) 4. Two or more dispensings for acute migraine-specific treatments, 7-180 days apart (50,000 patients) 5. One or more claim for migraine and a visit to a neurologist (30,000 patients) In addition, epilepsy diagnoses during baseline resulted in exclusion	This algorithm identified one third of the general population as having migraine. Acute migraine-specific treatments were triptans and ergotamines. Not validated.
Pavlovic, Yu [46]	Researchers used a structured interview to diagnose chronic migraine among patients with a diagnosis claim for migraine but without a diagnosis claim for chronic migraine from a large medical group in California. Per the selected algorithm, patients were identified as having undiagnosed chronic migraine if their probability of having chronic migraine was 0.55 or larger based on coefficients from a logistic regression model and their individual-level values for 4 variables measured in a 12-month period: having 15 or more claims for acute migraine medications, having 24 or more health care visits, being a female, and having claims for 2 or more preventive medication classes.	Prevalence of migraine cannot be ascertained. This algorithm was validated: sensitivity was 78% and specificity was 73%.
Skajaa, Szépligeti [29]	Using the Danish nationwide registries, the authors identified pregnancies in women with migraine as "pregnancies among women with a diagnosis of migraine during a hospital encounter (inpatient, outpatient, or emergency) between 1-Jan-1995 and the date of pregnancy end, or with at least 2 outpatient dispensings of a migraine-specific acute or preventive medication between 1-Jan-2004 and the date of pregnancy end." The authors' comment: "Medication proxies were used to identify migraine diagnoses not resulting in a hospital contact, because diagnoses in the primary health care sector are not captured in Danish registries."	This resulted in a prevalence of about 9.5% among pregnant women. Not validated.

Author (year)	Algorithm	Comments
Wood, Burch [48]	Using MarketScan, the authors identified migraineurs among pregnant women as women who met at least 1 of the following criteria: Primary definition: Two or more 346.xx ICD-9-CM codes in the 90 days before LMP One or more 346.xx ICD-9-CM codes in the 90 days before LMP and a prescription for migraine One or more 346.xx ICD-9-CM codes in the 90 days before LMP and a neurology encounter Two or more 346.xx ICD-9-CM codes at any time during the study period and a neurology encounter Secondary definition: 1 or more 346.xx ICD-9-CM codes in the 90 days before LMP	ICD codes were mostly sought for in the 90 days before the LMP. The primary definition of migraine resulted in a prevalence of about 1% The secondary definition (expected to be very sensitive) resulted in a prevalence of 1.3% Not validated.

ED = emergency department; ICD = International Classification of Diseases; ICD-9-CM = International Classification of Diseases, 9th edition, Clinical Modification; LMP = first day of last menstrual period.

For this study, we propose to identify migraine as described in Table 4. This algorithm is a variation of those by Hoffman, Xue [22] and Yusuf, Chia [36] that incorporates ICD-10-CM codes and new migraine-specific medications, relaxes the time interval for subsequent codes in light of the findings by Kolodner, Lipton [47], and removes a nonspecific criterion that resulted in a very large prevalence. This algorithm is generally aligned with the algorithm proposed by Wood, Burch [48] but with a broader interval for code identification and without the nonspecific criterion related to a visit to the neurologist.

Table 4. Identification of Patients with Migraine in this Study

Item	Description
Algorithm elements	
Migraine codes	ICD-10-CM: G43.xx (any code nested in G43) In the primary or another position
Migraine-specific treatments	Triptans, ergotamines, gepants, ditans, CGRP monoclonal antibodies (note: use of some of these treatments in a specified period determines exclusion from this study [Section 4.2.1.3]).
Period to identify migraine codes and migraine-specific treatments	Any time since Jan-2016 through the end of pregnancy (note: this requires that pregnancies have been identified before migraine is ascertained). The minimum period of enrollment with medical and pharmacy benefits before pregnancy is specified in Section 4.2.1.

Item	Description
Algorithm criteria	
Patients meeting 1 or more of the following criteria will be considered as having migraine: 1. One or more inpatient claim for migraine and 1 or more outpatient/ED claim for migraine at least 7 days apart within 1 year, including all the time prior to the estimated date of LMP and through pregnancy 2. One or more inpatient claim for migraine and 1 or more dispensing for a migraine-specific treatment at least 7 days apart within 1 year, including all the time prior to the estimated date of LMP and through pregnancy 3. Two or more outpatient/ED claims for migraine at least 7 days apart 4. One or more outpatient/ED claim for migraine and 1 or more dispensing for a migraine-specific medication at least 7 days apart 5. Two or more dispensings for migraine-specific treatments at least 7 days apart	

CGRP = calcitonin gene–related peptide; ED = emergency department; ICD-10-CM = *International Classification of Diseases, 10th Revision, Clinical Modification*; LMP = first day of last menstrual period.

4.2.1.3 Inclusion and Exclusion Criteria in Study Groups

All pregnant women aged 16 to 49 years, inclusive, at the estimated date of LMP within the study observation period are eligible to enter in the study.

A pregnant woman who fulfills 1 or more of the following criteria will be excluded from the study:

- Insufficient information to estimate the date of LMP (e.g., no recorded outcome of pregnancy)
- Has at least 1 pharmacy dispensing for ditans (i.e., lasmiditan) within a 5–half-life time window prior to the estimated LMP date or any time during pregnancy
- Has at least 1 pharmacy dispensing for CGRP receptor antagonists other than rimegepant (i.e., ubrogepant) within a 5–half-life time window prior to the estimated LMP date or any time during pregnancy
- Has at least 1 pharmacy dispensing for CGRP monoclonal antibodies (i.e., erenumab, fremanezumab, eptinezumab, and galcanezumab) within a 5–half-life time window prior to the estimated LMP date or any time during pregnancy

The reasons for the exclusion of ditans, CGRP receptor antagonists other than rimegepant, and CGRP monoclonal antibodies from the study groups are as follows:

- The unknown pregnancy safety profile of these new migraine therapies, which are being studied via other pregnancy exposure registries
- The challenge that concomitant use of rimegepant and these medications presents for interpreting results and detecting a possible safety signal for rimegepant
- The low likelihood that multiple CGRP medications and/or ditans will be used within a single pregnancy, either concurrently or in sequence, due to prescriber concerns over the unknown safety profiles of these medications and payer reimbursement

However, the exclusion of pregnant women exposed to ditans and CGRP monoclonal antibodies will be evaluated during the annual monitoring of study size. The potential inclusion of pregnancies exposed to these medications will be considered, if deemed necessary to reach the target study size (see Section 9.5).

Antiemetic medications and calcium channel blockers will not be included among the medications that determine entry into the primary comparator group. Antiemetic medications are more likely used in pregnancy for morning sickness than for migraine, and calcium channel blockers are not recommended for the treatment of migraine by existing guidelines. Regarding antiemetic medications, 2 have been noted to be used for migraine in pregnancy: ondansetron and metoclopramide [40]. Ondansetron is not approved for migraine in the US [49], but it is widely used in pregnancy as an antiemetic: 13% of women used it in the first trimester in 2013-2014 to treat morning sickness in a study in the US, and the prevalence of use was increasing [50]. Arguably, ondansetron might be more commonly used in pregnancy for morning sickness than for migraine. Metoclopramide is approved for gastroesophageal reflux and gastroparesis in the US [51]. Patterns of use in pregnancy in the US, peaking in the first trimester, which are relatively high in the second trimester and lower in the third trimester and before pregnancy, suggest that most of its use is related to nausea and vomiting in pregnancy [52]. Calcium channel blockers have been listed as drugs that can be used for the treatment of migraine in pregnancy [40]; however, the American Academy of Neurology [53] and, more recently, the American Association of Family Physicians [23] did not find evidence to support the use of drugs in this class for migraine prevention in adults.

Finally, the inclusion and exclusion criteria that will determine the inclusion in each study group are described below.

4.2.1.3.1 Rimegepant-exposed Group

The rimegepant-exposed group will include pregnant women with migraine treated with rimegepant who fulfill the following criteria:

- Has a migraine diagnosis that meets the criteria in Table 4 any time prior to the estimated LMP date or during pregnancy
- Has at least 1 pharmacy dispensing for rimegepant within 30-day time window prior to the estimated LMP date (see Section 4.3.1) or any time during pregnancy.

4.2.1.3.2 Primary Comparator Group

The primary comparator group will include pregnant women with migraine exposed to medications for the treatment of migraine other than rimegepant. Pregnant women will fulfill all the following inclusion and exclusion criteria:

- Inclusion criteria:
    - Has a migraine diagnosis that meets the criteria in Table 4 any time prior to the estimated LMP date or during pregnancy
    - Has at least 1 pharmacy dispensing for a medication indicated for the treatment of migraine within 30-day time window before the estimated LMP date (see Section 4.3.1) or any time during pregnancy. Medications indicated for the treatment of migraine include NSAIDs, acetaminophen, triptans, ergots, opioids, beta-blockers, anticonvulsants, antidepressants, and botulinum toxin (Annex 3, Table 11)
- Exclusion criterion:
    - Has at least 1 pharmacy dispensing for rimegepant within 30-day time window prior to the estimated LMP date or any time during pregnancy

4.2.1.3.3 Secondary Comparator Group

The secondary comparator group will include rimegepant-unexposed pregnant women without migraine. Pregnant women will fulfill all the following inclusion and exclusion criteria:

- Inclusion criterion
    - Has no migraine diagnosis that meets the criteria in Table 4 any time prior to the estimated LMP date or during pregnancy
- Exclusion criterion:
    - Has at least 1 pharmacy dispensing for rimegepant within 30-day time window prior to the estimated LMP date or any time during pregnancy

For the analysis of MCM, additional exclusion criteria for the rimegepant-exposed and comparator groups will be applied (see Section 4.3.2):

- Women and linked infants exposed to medications of known teratogenic risk within a 5–half-life time window prior to the estimated LMP date or during pregnancy (Annex 3, Table 12)

- Women and linked infants that experience infections known to cause congenital anomalies during pregnancy
- Women and linked infants with syndromic or chromosomal anomalies identified during pregnancy or at birth

4.2.2 Study Period

Start of study observation period: The study start date is the date when rimegepant is first available in the participating US data source. Rimegepant was approved by the FDA on 27-Feb-2020. The planned start date is 16-Mar-2020, coinciding with the availability of rimegepant in the US.

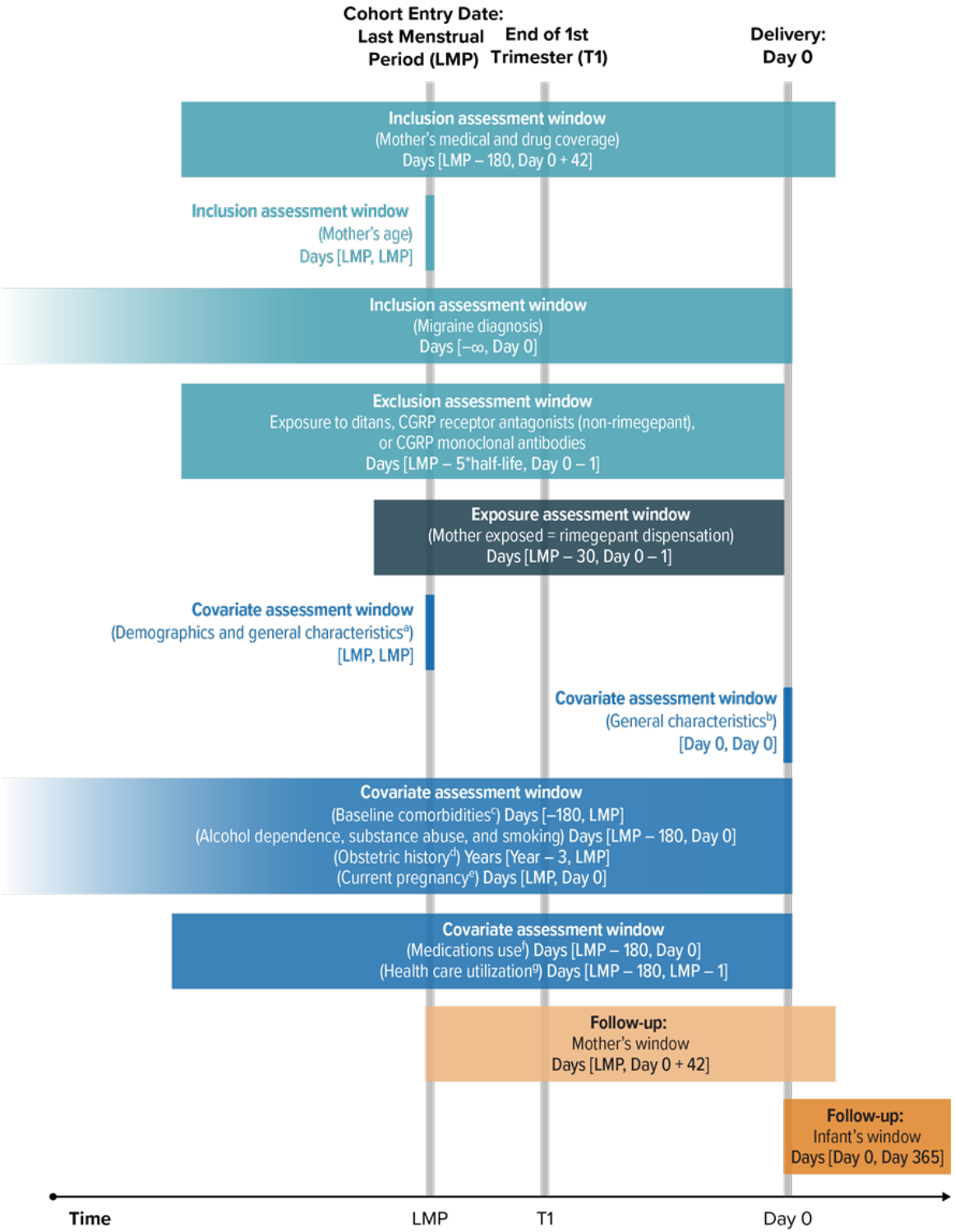
End of study observation: The end of study observation is the date when the final data point has been collected from the data source following fulfillment of the target study size, expected in 2027.

4.2.3 Follow-up

The study group entry date (i.e., index date) is the estimated date of LMP. This date is considered as the beginning of the pregnancy. The baseline period will comprise all the period available in the mother's record from Jan-2016 prior to and including the estimated LMP date. The pregnancies will be followed from the estimated date of LMP through the end of pregnancy plus a 42-day postpartum period until a pregnancy outcome is identified. The follow-up period will vary according to the outcome evaluated. Infants will be followed from the date of birth up to 12 months.

An overview of the study design is depicted in Figure 2.

Figure 2. Design Diagram of the Rimegepant Post-authorization Safety Study



CGRP = calcitonin gene–related peptide; LMP = first day of last menstrual period; MCM = major congenital malformation; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; SGA = small for gestational age; TORCH = toxoplasmosis, syphilis, varicella zoster, parvovirus B19, rubella, cytomegalovirus, herpes.

a Age (years) at the beginning of pregnancy, duration of health plan enrollment prior to pregnancy, calendar year of pregnancy at the estimated date of LMP, and geographic region.
b Calendar year of end of pregnancy.
c Depression and bipolar disorder, anxiety and panic disorders, schizophrenia, epilepsy and seizures, cluster headache, hyperlipidemia, diabetes, hypertension, malignancy (all available data before the estimated LMP date), thyroid disease, respiratory disease, including asthma, liver disease, chronic kidney disease, obesity, cardiovascular diseases.
d Obstetric history: gravidity, parity, history of spontaneous abortions, pregnancy termination, preterm births, live births with MCM, stillbirths, SGA, gestational diabetes, and gestational hypertension in previous pregnancies.
e Current pregnancy characteristics: multiple pregnancy, gestational diabetes, gestational hypertension; TORCH infections, and SARS-COV-2 infection.
f Use of medications of known teratogenic potential, preventive migraine drugs (topiramate, other anti-epileptics, cardiovascular medications, antidepressants, botulinum toxin), acute migraine drugs (triptans, ergotamine derivatives, prescription nonsteroidal anti-inflammatory drugs, opioids), acute and preventive cluster headache drugs, prescription cannabinoids, antipsychotics, oral antidiabetics, insulin, antihypertensive medications, lipid-lowering drugs, antithyroid medications, antiplatelet agents, anticoagulants, antiemetics and antinauseants, and other medications.
g Number of office visits, telemedicine encounters, number of emergency department visits, and number of hospitalizations.

4.3 Variables

All available data prior to the start of the pregnancy will be used to assess baseline characteristics. Claims will be used as the data source for exposure status, outcomes, and covariates, as available.

4.3.1 Exposure

The exposure of interest is rimegepant; in addition, for the primary comparator group, the exposure(s) of interest are other medications indicated for the treatment of migraine (see Section 4.2.1.3). Medications for acute treatment of migraine are used on an "as needed" basis to stop a migraine attack as quickly as possible. Preventive migraine medications are generally taken daily or every other day (rimegepant), and acute medications may be used concomitantly for breakthrough migraines.

The time window for ascertainment of exposure to rimegepant will include a period of 30 days prior to the estimated LMP date until the end of pregnancy for end-of-pregnancy and infant outcomes. In a review of the ORD for the period 01-Feb-2020 through 31-Dec-2020, 415 women aged 16-49 years had received a median of 2 rimegepant dispensings per woman (Q1-Q3, 1-3); among those that had more than 1 rimegepant dispensing, the median number of days between dispensings was 31 days (Q1-Q3, 26-42). The length of the period prior to the estimated LMP date will be further confirmed based on the analysis of patterns of use of rimegepant annually during the monitoring phase as described in Section 4.7.2. A 6-month period prior to the estimated LMP date will be used to determine the pattern of use of rimegepant. The median number of days between consecutive dispensings of rimegepant within this period will be calculated among all pregnant women with rimegepant dispensings (hereafter, "median interval"). The number of days between dispensings has been proposed as a preferred method to assign the duration of prescriptions when this information is not available [54,55], as is the case for medications to be taken as needed. Hence, the median interval will be used to confirm or adjust

the 30-day time window before the LMP date for assessing the potential exposure of the pregnancy to rimegepant. If adjustment is needed, the exposure window for rimegepant will start 1 median interval before the estimated LMP date and will end at the end of pregnancy. A pregnancy will be considered exposed to rimegepant if 1 or more pharmacy dispensings occur within this period [54]. For the analyses of congenital malformations, the exposure window will include the defined time before the estimated LMP date until the end of the first trimester of pregnancy. For analyses on spontaneous abortions or elective terminations, the exposure window will start at the defined time before the estimated LMP date and extend to the end of pregnancy for pregnancies ending in spontaneous abortion or elective termination and will end at 20 gestational weeks for pregnancies that do not end in those outcomes, which roughly coincides with the period of ascertainment of these outcomes (i.e., < 20 gestational weeks).

Similarly, for the primary comparator group, for medications other than rimegepant that are indicated for the acute or preventive treatment of migraine, the exposure window will include a 30-day period before the estimated LMP date. This period will be evaluated annually during the monitoring phase, as described in Section 4.7.2. Specifically, the median number of days between consecutive dispensings of each type of medication (by medication category) will be obtained and determine the need to adjust the 30-day exposure window. A pregnancy will be considered exposed if a pharmacy dispensing for any of these medications occurs within the defined period for each medication category. Medications dispensed before the defined period prior to the estimated LMP date will not be considered in determining the entry into the primary comparator group.

A woman may contribute to the study with more than 1 pregnancy over the course of the study period. Each pregnancy will be allocated to the corresponding exposure group based on the defined windows for exposure ascertainment, so that a woman may contribute to more than 1 study group (i.e., 1 pregnancy can contribute to only 1 exposure group), but a second pregnancy can contribute to a different exposure group.

Exposure will be defined based on information from 1 or more dispensed prescriptions (treatment initiation or continuation) with dispensing dates recorded within the defined exposure windows. Sensitivity analyses with varying exposure windows and subgroup analyses—stratified by patterns of use that correspond to acute only, preventive only, or acute and preventive use of rimegepant—will be conducted (see Section 4.7.6 and Section 4.7.7) The sources for ascertainment of medication use will be pharmacy claims.

To validate the proposed approach to determine the exposure status, a patient survey will be conducted separately among a sample of women of childbearing age identified in the ORD who are users of rimegepant or of other medications for migraine. This will be a one-time survey to be conducted after approximately 2 years of availability of rimegepant for preventive treatment of migraine in the data source. This period will allow for a relatively large number of users and a well-established use of rimegepant for acute and preventive treatment. It is anticipated that the survey results will be available at the time of the 2025 interim report.

4.3.2 Study Outcomes

Study outcomes will be identified based on the ICD-10 diagnosis and procedure, CPT, or HCPCS codes recorded in medical claims.

Definitions of outcomes will be based on published, validated algorithms to the extent possible based on the available information. Study outcomes will be ascertained from outpatient and inpatient records available from the data source. To date, some published algorithms are based on *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes, and no published validated algorithms based on ICD-10 codes in US claims data are available. If such algorithms become available over the course of the study and have acceptable validation results (e.g., positive predictive value point estimate ≥ 70%), they will be used in the study. The validation process will be detailed in the data validation plan, along with the strategy for estimating the target number of events for validation and the strategy for sampling events.

4.3.2.1 Medical Record Procurement and Adjudication

Among the identified claims-based outcomes, medical records will be sought for case confirmation. A chronological listing of relevant claims will be reviewed for each of the potential cases in order to determine the medical site of treatment, and at least 1 alternate site, most likely to yield medical records with the necessary information to confirm case status.

Medical record procurement will be undertaken to confirm outcomes that meet the criteria of the claims review process. Optum, in collaboration with a clinician(s), will develop a medical record review form that will include clinical elements necessary to confirm the outcome diagnosis. Providers will be asked to send all available medical information occurring during the period of interest (i.e., surrounding the service date of the relevant claim). This will include, but is not limited to, the following types of information:

- Office visit notes
- History and physical exam reports
- Laboratory reports
- Diagnostic imaging reports
- Labor and delivery records
- Hospital discharge summaries
- Surgical reports
- Histology/pathology reports
- Consultation/specialist notes

For each potential case, 1 medical record will be requested from 1 provider. If a medical record cannot be obtained from a primary provider, Optum will contact the alternate provider(s). Of those that are requested, approximately 70%-85% of the medical records are expected to be successfully obtained [56,57]. Optum will contract with 2 clinical consultants with expertise in the field of clinical genetics for the adjudication of malformations, and 2 clinical consultants with expertise in obstetrics for the adjudication of spontaneous abortions, fetal deaths/stillbirths, and small-for-gestational-age births. All medical records for pregnancies with the claims-based outcomes of MCM, spontaneous abortion, fetal deaths/stillbirth, or elective termination will be reviewed for mention of MCMs, as pregnancies that do not result in live births may not have MCMs captured in medical claims. The clinicians (blinded to the maternal use/receipt of migraine treatments) will review the medical record for each potential case and adjudicate the outcomes. Each record will be independently adjudicated by 2 clinicians, and consensus will be sought for any discrepancies in adjudication results between the clinicians. Optum will work with the contracted clinicians to arrive at consensus, and a third independent adjudicator will be available to resolve discrepancies or break ties in adjudication results, if needed.

4.3.2.2 Pregnancy Outcomes and Pregnancy Complications

Pregnancy outcomes and pregnancy complications will be ascertained in medical claims in the mother records:

4.3.2.2.1 Primary Pregnancy Study Outcomes

- Spontaneous abortion [pregnancy loss at < 20 completed weeks [58]]. The time period for ascertainment will be the first 20 weeks following the estimated date of LMP. Abortion events with codes for ectopic pregnancy will not be considered events of spontaneous abortion.

- Fetal deaths/stillbirth (≥ 20 completed weeks). Fetal death refers to the spontaneous intrauterine death of the fetus during pregnancy. Earlier fetal deaths will be considered spontaneous abortions (< 20 completed weeks). Fetal death/stillbirth are intrauterine deaths that occur at 20 weeks or later in the pregnancy.

4.3.2.2.2 Secondary Pregnancy Study Outcomes

Elective termination: the reason for termination (e.g., therapeutic abortion, abnormal findings in fetus in prenatal tests, ectopic pregnancy) will be ascertained to the extent to which data are available. The time period for ascertainment will be the first 20 weeks following the estimated date of LMP or until abortion.

Pre-eclampsia and/or eclampsia during pregnancy. The time period for ascertainment will be any time during pregnancy.

4.3.2.3 Fetal/Infant Outcomes

Fetal/infant outcomes will be evaluated on infants successfully linked to mothers. Outcomes will be ascertained on either medical claims in the infant record during the first year after birth or medical claims in the mother's record between the beginning of pregnancy and the end of the immediate postpartum period (42 days).

4.3.2.3.1 Primary Fetal/Infant Study Outcomes

- Major congenital malformations. Definitions and potential groupings will be based on the Metropolitan Atlanta Congenital Defects Program (MACDP) classification [59,60]. Congenital cardiac anomalies that are classified as critical (i.e., cyanotic defects, as well as hypoplastic left heart syndrome and pulmonary atresia) will be included among the MCM study outcome. Transient cardiac defects (i.e., patent foramen ovale, ventricular septal defect, and persistent ductus arteriosus) in term infants will be also included in the MCM study outcome because certain transient defects may be associated with maternal medication exposure in pregnancy and can vary by age of detection and/or age of resolution [61]. However, transient cardiac defects in preterm births will be excluded from the definition of MCM outcome because these malformations are often physiologically expected in preterm births or are found as a result of improved technology and have little clinical significance for a large proportion of cases.

  Prematurity-related anomalies (e.g., patent ductus arteriosus, undescended testes in infants delivered at < 37 gestational weeks) and positional birth defects (e.g., torticollis, hip dislocation in infant in breech position) will not be included in the definition of MCM outcome.

  Depending on the number of events observed, specific categories of MCMs (e.g., cardiovascular) and specific malformations (e.g., hypospadias, cleft lip with or without cleft palate, and cardiac malformations) will be explored.

- Small for gestational age, defined as a birth weight below the 10th percentile for the gestational age at birth, identified by diagnosis codes for small-for-gestational-age births and for birth weight. The period for ascertainment will be the first month after delivery in the mother's record or 1 month after birth in the infant's record.

4.3.2.3.2 Secondary Fetal/Infant Study Outcomes

- Preterm birth (birth at < 37 completed weeks of gestation). Preterm birth can be identified either from the maternal records up to 1 month after delivery or from the linked infant's record within 1 month after birth.

Pregnant women and linked infants with identified syndromic or chromosomal anomalies (i.e., Down syndrome; trisomies18 and 13, and other trisomies; monosomies, and deletions from the autosomes; balanced re-arrangements and structural markers; Turner's syndrome, other sex chromosome abnormalities, and other chromosomal abnormalities), will not be included in the

analysis of major congenital anomalies. Also, pregnant women and linked infants with prenatal exposure to medications with known teratogenic risk in the first trimester of pregnancy (see list of medications in Annex 3, Table 12) [62] or with prenatal exposure to infections known to cause malformations will not be included in the analysis of MCM (Section 4.2.1.3).

Table 5 presents the algorithms proposed for identification of study outcomes. Currently, no validation studies of claims-based algorithms utilizing ICD-10 codes for pregnancy and infant outcomes have been published in the literature. If applicable validation studies are published during the conduct of this study, claims-based algorithms for the identification of outcomes will be updated accordingly, assuming that the published algorithms for the study outcomes are shown to perform well (positive predictive value ≥ 70%). These claims-based algorithms will be used to identify study outcomes in lieu of medical record review, except for MCMs, for which all cases will be confirmed through medical record review (see Section 4.3.2.1).

Table 5. Algorithms for the Identification of Outcomes

Outcome	Algorithm	Pregnancies in Which the Outcome Will Be Ascertained	Window for Outcome Ascertainment	Maternal or Infant Record	Validity
Spontaneous abortion	Assignment of final pregnancy outcome as spontaneous abortion per the data source–specific pregnancy-identification algorithm	All pregnancies	< 20 completed weeks of gestation	Maternal record	
Fetal deaths/ stillbirth	Final pregnancy outcome of stillbirth as assigned by the data source–specific pregnancy-identification algorithm	All pregnancies	≥ 20 completed weeks of gestation	Maternal record	
Elective termination	Final pregnancy outcome as termination or ectopic, or molar pregnancy per the data source–specific pregnancy-identification algorithm	All pregnancies	< 20 completed weeks of gestation	Maternal record	
Pre-eclampsia/ eclampsia	Pre-eclampsia: ≥ 1 maternal ICD-10-CM diagnostic code O14x recorded in inpatient or other therapy claims or during the delivery hospitalization or Eclampsia: ≥ 1 maternal ICD-10-CM diagnostic code O15x recorded in inpatient or other therapy claims or during the delivery hospitalization	All pregnancies	Any time during pregnancy and through 42 days after end of pregnancy	Maternal record	Pre-eclampsia validated algorithm based on ICD-9-CM codes 642.4x, 642.5x, 642.6x, 642.7x, showed a PPV of 82% (95% CI, 70%-91%) [63]
Major congenital malformations	At least 1 ICD-10-CM diagnosis code for MCM in infant claims based on the definitions of the Metropolitan Atlanta Congenital Defects Program	Pregnancies with live birth, with linked infant	From birth through 365 days after birth	Infant record	
Small for gestational age	≥ 1 maternal or infant ICD-10-CM diagnostic code recorded in inpatient or other therapy claims from delivery to delivery + 30 days	Pregnancies with live birth, with linked infant	From date of delivery through 30 days after delivery	Maternal and infant record	Validated algorithm based on ICD-9-CM diagnostic code 656.5x, 764.0x, 764.1x, 764.9x showed a PPV of 92%

Outcome	Algorithm	Pregnancies in Which the Outcome Will Be Ascertained	Window for Outcome Ascertainment	Maternal or Infant Record	Validity
					(95% CI, 82%-97%) [63]
Preterm birth	Algorithm A: At least 1 maternal or infant ICD-10-CM diagnosis code for preterm birth, low birth weight, or specific conditions more common in preterm infants Algorithm B: At least 1 maternal or infant ICD-10-CM diagnosis code for gestational age in weeks corresponding to < 37 weeks at birth Algorithm C: Meets criteria for either Algorithm A or Algorithm B	Pregnancies with live birth, with linked infant	< 37 completed weeks of gestation Algorithm A within 0-30 days after pregnancy end date Algorithm B: Maternal codes must be within 0-7 days before pregnancy end; infant codes must be within 0-30 days after pregnancy end date	Maternal and infant record	Algorithm A is adapted from a published algorithm that included only codes designated for use in infants [64]. For the present study, the ICD-9 codes in that algorithm will be mapped to ICD-10-CM codes ICD-10-CM maternal codes for preterm delivery will also be included in this study because their ICD-9-CM equivalents have been validated in the US, with PPV of 92% (95% CI, 87%-98%) in infants' claims data and of 76% (95% CI, 64%-88%) in mother's claims [65]

CI = confidence interval; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; ICD-9 = International Classification of Diseases, 9th Revision; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; MCM = major congenital malformation; PPV = positive predictive value; US = United States.

4.3.3 Other Variables

For pregnant women in each study group, the variables listed below will be ascertained using information available in the mother's medical record during the period prior to pregnancy and during pregnancy. The period for ascertaining baseline characteristics will be limited by the period of enrollment in the health care plan. For most variables, no missing values are expected. For variables related to patients' medical history or drug exposure, the absence of a diagnosis code for a condition is interpreted as the absence of the condition, and the absence of medication claims is interpreted as the absence of exposure to those medications. Obesity, smoking, alcohol abuse and drug abuse are ascertained through codes (including proxies) and may be under-recorded (Section 4.7.4). The variables listed below were selected to provide a general description of the characteristics of the study groups and to explore potential confounding. The definitions and period of ascertainment for these variables is described in Annex 3, Table 13.

Demographic and general characteristics:

- Age (years) at the beginning of pregnancy
- Duration of health plan enrollment prior to pregnancy
- Calendar year of pregnancy at the estimated date of LMP
- Calendar year of end of pregnancy
- Geographic region (Northeast, West, Midwest, South)

Prior history of medical conditions will be identified based on *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) diagnosis codes within a look-back period of 6 months before the estimated LMP date and including LMP date, except where indicated, and through the end of pregnancy where indicated (see in Annex 3, Table 13):

- Depression and bipolar disorder
- Anxiety and panic disorders
- Schizophrenia
- Epilepsy and seizures
- Alcohol dependence, using proxies based on diagnoses and specific treatments
- Substance abuse, using proxies based on diagnoses and specific treatments
- Hyperlipidemia
- Diabetes

- Hypertension
- Malignancy, within a look-back period that can extend from Jan-2016 to and including LMP date
- Thyroid disease
- Respiratory disease, including asthma
- Liver disease
- Chronic kidney disease
- Obesity, using diagnoses and specific treatments or procedures, as available in medical claims
- Smoking, use proxies based on diagnoses and specific treatments, as available in medical claims
- History of cardiovascular diseases, including myocardial infarction, transient ischemic attack, ischemic stroke, ischemic heart disease, angina, heart failure, cardiac arrhythmia, hemorrhagic stroke, peripheral vascular disease
- Cluster headache

Migraine type, with or without aura, and with or without intractable pain, as available, will be identified based on ICD-10-CM diagnosis codes within a look-back period from Jan-2016 through the end of pregnancy.

Prior obstetric history will be identified based on ICD-10-CM diagnosis codes and procedure codes within a look-back period of up to 3 years:

- Gravidity, the number of pregnancies prior to the current pregnancy
- Parity, the number of live births prior to the current pregnancy
- Spontaneous abortions, history of spontaneous abortions in previous pregnancies
- Pregnancy termination, history of previous terminated pregnancies
- Preterm births, history of preterm births prior to the current pregnancy
- Live births with MCMs, history of pregnancies with live births with MCMs prior to the current pregnancy
- Stillbirth, history of pregnancies with stillbirth prior to the current pregnancy

- Small for gestational age (SGA), history of deliveries with codes indicative of SGA
- Gestational diabetes, gestational diabetes during pregnancy(s) prior to the current pregnancy
- Gestational hypertension, gestational hypertension during pregnancy(s) prior to the current pregnancy

Comedication use will be ascertained separately in the 6 months prior to the estimated LMP date and during pregnancy. Medications will be identified based on National Drug Codes, or HCPCS codes, as applicable (Annex 3, Table 13):

- Use of medications of known teratogenic potential (Annex 3, Table 12)
- Use of prescription cannabinoids
- Preventive cluster headache drugs
- Acute cluster headache drugs
- Antidepressants
- Antipsychotics
- Oral antidiabetics
- Insulin
- Antihypertensive medications
    - Calcium channel blockers
    - Angiotensin-converting enzyme inhibitors
    - Angiotensin II antagonists
- Lipid-lowering drugs
- Antithyroid medications
- Antiplatelet agents
- Anticoagulants
- Antiemetics and antinauseants
- Other medications associated with the medical conditions identified previously

Use of preventive migraine drugs will be ascertained separately in the 6 months prior to and during pregnancy: topiramate, other anti-epileptics, beta-blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitor, and botulinum toxin. The list of specific medications is shown in Annex 3, Table 11.

- Number of users of each medication, number of different medications, number of prescriptions, time (days) between consecutive prescriptions

Use of acute migraine drugs will be ascertained separately in the 6 months prior to and during pregnancy: triptans, ergotamine derivatives, prescription NSAIDs, aspirin, acetaminophen, and opioids. The list of specific medications is shown in Annex 3, Table 11.

- Number of users of each medication, number of different medications, number of prescriptions, time (days) between consecutive prescriptions

Health care utilization will be ascertained within the 6-month period prior to the beginning of the pregnancy:

- Number of office visits
- Number of telemedicine encounters
- Number of emergency department visits
- Number of hospitalizations

Characteristics of the current pregnancy:

- Multiple pregnancy
- Gestational diabetes
- Gestational hypertension
- TORCH infections during pregnancy
- SARS-COV-2 infection during pregnancy

4.4 Data Sources

The selection of the appropriate data source (i.e., research partner and database provider) for the study was based on a feasibility assessment. The availability of the required information for the study on exposures, patient characteristics, and outcomes; access to mother-infant linked data; and ability to support outcome validation through access to medical record review and abstraction were key features to determine the fitness for purpose.

The patients included in this study will be drawn from the ORD, a proprietary research database that contains the eligibility data, medical claims, and pharmacy claims from a large, commercial health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US and comprise approximately 3% to 4% of the US population.

Optum research activities use de-identified data from the ORD. For a subset of patients in the ORD with administrative approval from the health plan, patient-identifiable information may be accessed for further inquiries, including medical chart review. Patient-identifiable information is available for about 40% of the membership and can be accessed only after approval of the study protocol by an appropriate institutional review board (IRB) and privacy board. All data access conforms to applicable Health Insurance Portability and Accountability Act policies.

Accessible information from the ORD includes demographics, pharmacy use, and all medical and facility claims, which provide data on services and procedures and their accompanying diagnoses.

The coding of medical claims conforms to insurance industry standards, including the following features:

- Use of designated claims forms (e.g., physicians use the Health Care Financing Agency 1500 form, and hospitals use the UB-04 or UB-92 form)
- International Classification of Diseases, 9th Revision (ICD-9) codes
- International Classification of Diseases, 10th Revision codes
- Current Procedural Terminology codes
- Healthcare Common Procedure Coding System codes
- Cost information
- De-identified patient and provider codes

Claims for pharmacy services are typically submitted electronically by the pharmacy at the time prescriptions are filled. Pharmacy claims data allowing longitudinal tracking of medication refill patterns and changes in medications include the following information:

- National Drug Code
- Drug name
- Dosage form
- Drug strength
- Fill date

- Days of supply
- Cost information
- De-identified patient and prescriber codes

An important advantage of the ORD is the large number of patients that can be studied because the data are routinely collected and maintained in computerized data files. The completeness of the data allows investigators to link any number of patient, physician, and treatment attributes while maintaining the de-identified nature of the data. The database also captures a longitudinal record of medical services, irrespective of treatment site.

This study will employ the Optum DAPI, a proprietary process that includes a set of capabilities and established algorithms that is applied to claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link mothers' and infants' data in an ongoing manner within the ORD [66]. The algorithms are based on a combination of validated algorithms as reported in the literature and clinical input. Estimates from recent years show that in total, approximately 1.4 million pregnancies have been identified from 2007 through mid-2018 [67].

Mother and infant records will be linked through the presence of a common, unique family insurance identification number. This number is used by health plans to identify all members of a family who are covered by the same insurance plan for the purposes of defining coverage, payment, and reimbursement, providing assurance that mother-infant pairs identified in this manner are accurate. In addition, we require that claims relating to a delivery are within 10 days of the infant's birthdate.

Approximately 80,000-100,000 pregnancies are identified each year within the database. Of these, approximately 80% can be linked to an infant. These linkages enable proactive monitoring of pregnancy outcomes to ascertain a range of outcome-specific risks associated with drug exposure during pregnancy. This linkage has been used to address regulatory questions by pharmaceutical companies about the effects of drugs on pregnancy [68,69].

The fraction of identified deliveries that cannot be matched to an infant is likely due to the infant being covered under a health insurance plan other than the mother's plan. This may occur if the newborn were to be added to the other parent's plan (rather than the mother's), if the parents were to switch from individual plans to family health plans, or if the mother were covered under her parent's policy (in which case a separate plan would need to be purchased for the infant). While the reasons for switching of the infants' health plans may be related to coverage for treatments relating to infant outcomes, reasons for switching are likely nondifferential with respect to maternal exposure to migraine treatments. Therefore, although estimates of risk or prevalence may be underestimated due to the switching of health plans, estimates of relative risk should be unbiased.

Because the linkage is made within an identifiable health insurance database affiliated with Optum, Optum can (with appropriate approvals) access medical records for mothers or infants in order to ascertain covariate information or to confirm outcomes.

4.5 Study Size

With a ratio of 1:3 for exposed to unexposed subjects, the minimum number of exposed pregnancies to provide 80% probability to reject the null hypothesis (relative risk [RR] = 1.0) at the alpha = 0.05 level for relative risks of 2, 2.5, 3 and 4 is presented in Table 6 for each study outcome. For the primary outcome MCMs with a prevalence of 3% in unexposed pregnancies, a study size of 464 rimegepant-exposed pregnancies with linked infants (and 1,392 in each comparator group) would provide 80% power to reject the null hypothesis if the true population relative risk were 2. If the true population relative risk were 2.5, a study size of 233 exposed pregnancies with linked infants (and 699 in each comparator group) would provide 80% power to reject the null hypothesis.

Table 6. Estimated Number of Rimegepant-exposed Subjects Needed to Have an 80% Probability of Rejecting the Null Hypothesis (RR = 1.0) at the *P* = 0.05 Level for True Relative Risks of 2, 2.5, 3, and 4

Outcome	Prevalence of Outcome	True Population RR[a]			
		2	2.5	3	4
Major congenital malformations[b]	3%[d]	464	233	146	77
Small for gestational age[b]	11.1%[e]	110	54	33	16
Preterm birth[c]	10.23%[f]	121	59	36	18
Abortion (spontaneous and therapeutic)[b]	16%[g]	70	33	20	9
Stillbirth[b]	0.4%[g]	3,620	1,829	1,151	619
Elective termination[c]	11.3 per 1,000 women aged 15-44 years[h]	1,268	639	402	215
Pre-eclampsia/eclampsia[c]	4.7%[i]	289	144	90	47

RR = relative risk.
Note: Numbers of rimegepant-exposed subjects represent the number of exposed pregnancies needed for the maternal outcomes (abortion, stillbirth, elective termination, pre-eclampsia/eclampsia) or the number of mother-infant pairs for live birth outcomes (major congenital malformations, small for gestational age, preterm birth).
[a] Assuming 80% power, alpha = 0.05, a ratio of exposed to unexposed subjects of 1:3. Calculations were done with PS: Power and Sample Size Calculation version 3.1.6, Oct-2018 [70].
[b] Primary outcome.
[c] Secondary outcome.
[d] CDC [71].
[e] Jensen, Foglia [72].
[f] Martin, Hamilton [73].
[g] Data provided by Optum (Optum Research Database, Oct-2015 through Sep-2020).
[h] Kortsmit, Jatlaoui [74].
[i] Fingar, Mabry-Hernandez [75].

To attain the study size needed for the primary outcome of MCM, the percentage of pregnancies ending in live births and the percentage of these pregnancies that are linkable to infant records need to be considered. This number is estimated at approximately 1,152 exposed pregnancies and 3,456 unexposed pregnancies in each of the 2 comparator groups based on the following assumption:

- 1,152 exposed and 3,456 unexposed pregnancies (in each of the 2 comparator groups)
- Of these, 62% would result in live births (714 exposed and 2,142 unexposed)
- Of these records, 65% would be linkable to infant records, resulting in 464 exposed and 1,392 unexposed newborns

Table 7 presents the minimum detectable risk estimates for each of the study outcomes with a study size of 464 rimegepant-exposed pregnancies with linked infants and 1,392 unexposed pregnancies with linked infants.

Table 7. Minimum Detectable Risk Estimate for Each Study Outcome With the Target Study Size

Outcome	Prevalence of Outcome	Minimum Detectable Relative Risk With 464 Rimegepant-exposed Pregnancies and Linked Infants[a]
Major congenital malformations[b]	3%[d]	2.00
Small for gestational age[b]	11.1%[e]	1.46
Preterm birth[c]	10.23%[f]	1.48
Abortion (spontaneous and therapeutic)[b]	16%[g]	1.36
Stillbirth[b]	0.4%[g]	4.66
Elective termination[c]	11.3 per 1,000 women aged 15-44 years[h]	2.83
Pre-eclampsia/eclampsia[c]	4.7%[i]	1.77

a Assuming 80% power, alpha = 0.05, a ratio of exposed to unexposed subjects of 1:3. Calculations were done with PS: Power and Sample Size Calculation version 3.1.6, Oct-2018 [70].
b Primary outcome.
c Secondary outcome.
d CDC [71].
e Jensen, Foglia [72].
f Martin, Hamilton [73].
g Data provided by Optum (Optum Research Database, Oct-2015 through Sep-2020).
h Kortsmit, Jatlaoui [74].
i Fingar, Mabry-Hernandez [75].

Actual study size will depend on medication uptake in the study data source, as well as on the observed percentage of live births among the study pregnancies and success of mother-infant record linkage. From previous experience with Optum DAPI, over 80% of pregnancies may result in live births, and over 85% of those can be linked to infant records [76]. In the period from

Oct-2015 through Sep-2020, 1,030,874 pregnancies were identified in the ORD, including 821,536 pregnancies (80%) with an observed outcome (i.e., evaluable pregnancies). These comprised 626,426 live births (76%) and 195,110 non-live births (24%). A total of 209,338 pregnancies exhibited no known outcomes that would conform to the primary or secondary outcomes at the time of the query (mostly because the woman disenrolled or the pregnancy was still ongoing). From Feb-2020 through 31-Dec-2020, 627 women had at least 1 dispensing of rimegepant in the ORD. Of these, 415 were aged 16 to 49 years and had a total of 864 dispensings collectively, with a median of 2 dispensings per women.

The feasibility of meeting the target study size will be assessed annually during the monitoring phase. Yearly counts, using all inclusion and exclusion criteria defined in the protocol for entry into the study groups, will inform whether the observed accrual of rimegepant-exposed pregnancies is sufficient to achieve the target study size. At the 2025 interim report, expected to include over 3 years of accrual of pregnancies in the study, if the projection indicates that the study size will be below the target size, in consultation with the FDA, a potential modification of the exclusion criteria to increase the study size will be considered. Specifically, the exclusion criterion related to use of ditans or CGRP monoclonal antibodies in pregnancy will be reassessed.

4.6 Data Collection and Management

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control (QC) checks of all programs. Each research partner will maintain any patient-identifying information securely on site according to internal standard operating procedures (SOPs) or guidance documents.

Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except select study staff.

Appropriate data storage and archiving procedures will be followed, with periodic backup of files. Standard procedures will be in place at each research center to restore files in the event of a hardware or software failure.

The research partner (Optum) will follow its own established procedures and generate results according to the analysis plan and specifications. The study will be carried out according to the Optum Epidemiology group's internal SOPs, which are consistent with the Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology (ISPE). In particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

All summary tables of results, and no individual patient identifiers, will be provided to RTI Health Solutions (RTI-HS), the coordinating center, which will compile the results and develop the report in collaboration with the research partner. RTI Health Solutions will follow its own QC procedures regarding transfer of data.

For requests to access data for audit purposes, only aggregated data from the research partner will be available at the coordinating center. The audit trail will consist of a detailed description of the methods to extract and process the electronic health records or claims data, as applicable. Access to raw data at the database research center will require the data requestor to obtain a license or apply for approval at a research committee and to fulfill the conditions required under the governance rules of the database research center.

4.7 Data Analysis

The description of the data analyses will be detailed in a statistical analysis plan. The statistical analysis plan will contain all operational aspects of the study described in detail, including the operational definitions of inclusion/exclusion criteria, exposure, outcomes, and covariates, with the corresponding lists of diagnoses, procedures, and medications codes. It will contain detailed descriptions of all analyses to be conducted and the corresponding shell tables. An overview is presented below.

4.7.1 Study Groups

The study groups are summarized in Table 8.

Table 8. Study Groups

	Exposed	Primary Comparator Group	Secondary Comparator Group
Study group definition	Pregnancies in women with migraine and exposure to rimegepant	Pregnancies in women with migraine exposed to other medications indicated for the treatment of migraine	Pregnancies in women without migraine
Migraine diagnosis	Required	Required	No diagnosis recorded in all available data in the period prior to the beginning of pregnancy or during pregnancy
Drugs	Required: Use of rimegepant within defined period of 30 days prior to the estimated LMP or any time during pregnancy (first trimester only for analysis of MCMs) No use of ditans, CGRP receptor antagonists other than rimegepant, or CGRP monoclonal antibodies within a 5–half-life time window before the estimated LMP and any time during pregnancy (first trimester only for analysis of MCM)	Required: No use of rimegepant within defined period of 30 days prior to the estimated LMP or any time during pregnancy Use of medications other than rimegepant that are indicated for the treatment of migraine within the defined period of 30 days before pregnancy or any time during pregnancy (first trimester only for analysis of MCMs) No use of ditans, CGRP receptor antagonists, or CGRP monoclonal antibodies within a 5–half-life time window before the estimated LMP and any time during pregnancy (first trimester only for analysis of MCMs)	No use of rimegepant within the defined period of 30 days prior to the estimated LMP or any time during pregnancy No use of ditans, other CGRP receptor antagonists, or CGRP monoclonal antibodies within a 5–half-life time window before the estimated LMP or any time during pregnancy (first trimester only for analysis of MCMs)

CGRP = calcitonin gene–related peptide; LMP = first day of last menstrual period; MCM = major congenital malformation.

4.7.2 Descriptive Analyses

All the analyses to be conducted to fulfill Objective 1 and Objective 2 will be descriptive, and no propensity score matching will be performed. For the descriptive analyses, the number of observations, mean, standard deviation, median, interquartile range, and range will be presented for continuous variables, and the number and percentage of patients in each category will be presented for categorical variables.

The study groups (exposed group, primary comparator group, and secondary comparator group) will be characterized based on the covariates listed in Section 4.3.3.

For Objective 1, the use of medications for migraine will be analyzed in the 6 months prior to the estimated LMP date, including the number of users; mean, standard deviation, median, and interquartile range of the number of dispensings; and the number of days between consecutive dispensings for each medication. These analyses will be included in the annual interim report.

For Objective 2, a description of the cohort attrition by eligibility criteria, selected characteristics of the pregnancies in each study group, and frequency of the study outcomes, will be reported for each study group in the annual interim report. Analyses based on claims-identified cases, including outcomes that have unvalidated algorithms and outcomes that have validated algorithms, will be presented.

4.7.3 Comparative Safety Analysis

For Objective 3, the safety comparative analyses, each pregnancy will be assigned a propensity score, a measure of the probability of receiving rimegepant versus a comparator drug (or no drug) given that patient's characteristics. This propensity score will either be used for matching rimegepant-exposed pregnancies to pregnancies in the comparator groups if sample size allows or included in multivariable models to reduce potential confounding of relative risk estimates (see Section 4.9).

Propensity scores will be estimated using logistic regression. The model will include only covariates that could act as potential confounders as independent variables, with rimegepant use/nonuse as the dependent variable. Only covariates assessed during baseline (i.e., prior to the estimated LMP date) and known (or highly suspected) to be confounders will be included in the propensity score model. A missing category for the potential confounders, when applicable, will be included when building the propensity score model. Variables for the propensity score modeling will include prespecified variables from Section 4.3.3, including demographic and general characteristics, prior history of medical conditions, prior obstetric history, comedication prior to LMP date, use of preventive migraine drugs prior to LMP date, use of acute migraine drugs prior to LMP date, and health care utilization. Characteristics of and medications used during the current pregnancy will not be included in the propensity score model. In addition, to ensure that important potential confounders are not inadvertently omitted, the most common diagnoses given, procedures administered, and drugs dispensed among the rimegepant-exposed group members will be identified using stepwise logistic regression. The list of these additional covariates will be reviewed by study researchers, and only those covariates that are known risk factors of adverse pregnancy/infant outcomes will be considered for inclusion in the propensity score model. Those covariates that are correlates of rimegepant use but are not risk factors for the outcomes (and therefore not confounders) will be removed from consideration. As some prespecified covariates may be closely correlated with the data-driven identified variables, correlations between prespecified and the data-driven defined covariates will be calculated. For variable pairs that are highly correlated (e.g., correlation > 0.9), one will be eliminated (retaining prespecified covariates where possible). In addition, univariate c-statistics will be evaluated for each variable remaining after examining correlations. The covariates will then be ranked by c-

statistic in descending order, and the data-driven identified variables with the highest c-statistics may be selected as covariates to be forced into the model. The remaining variables will be allowed to enter the propensity score model through the stepwise automatic variable forward selection procedure.

A single propensity score model will be used for all outcomes in comparisons of rimegepant-exposed pregnancies and pregnancies in the primary comparator group, and another propensity score model will be used for all outcomes in comparisons of rimegepant-exposed pregnancies and pregnancies in the secondary comparator group.

If the sample size is sufficient, rimegepant-exposed pregnancies will be matched separately to up to 3 pregnancies in each of the comparison groups on propensity score. Matching will be done based on a digit-based, greedy, nearest-neighbor matching process, in which exposed patients are matched, without replacement, to unexposed patients with the same propensity score at a given level of precision defined by the number of digits of the propensity score. When no further matches are available at a given level of precision, the number of digits is sequentially reduced, until a maximum allowable caliper of 0.1. This method has been shown to be an efficient approximation of nearest-neighbor matching. The caliper may be decreased in the case of insufficient balance following matching [77].

Balance of covariates will be assessed using the standardized difference comparing the matched study groups. Any variables with an absolute standardized difference > 0.1 may be considered unbalanced. If specific variables remain imbalanced after matching on the propensity score, they may be included as independent predictors in outcome models. Overall balance between the study groups, both before and after matching, will be assessed via overlap (or lack thereof) in histograms of the propensity scores.

Because the matching can result in the exclusion of some (unmatched) rimegepant-exposed pregnancies, alternative analysis methods may be considered. Namely, propensity scores (in continuous or categorical form) may be included in the outcome models or used in inverse probability of treatment weights [78]. These approaches can achieve similar levels of covariate control as matching, without the risk of excluding pregnancies due to a lack of suitable matches, but are broadly expected to produce similar results [79].

An advantage of matching is that “crude” results are adjusted for the matching variables. The main disadvantage is the loss of precision associated with the loss of unmatched subjects in the context of a rare exposure and rare outcomes. However, because many more pregnancies are expected in the 2 comparator groups unexposed to rimegepant, it is unlikely that rimegepant-exposed pregnancies will be left without appropriate matches. The variable-matching ratio has the advantage of minimizing the loss of exposed pregnancies due to lack of matches, while increasing precision due to multiple matches for easily matchable exposed pregnancies.

Comparative analyses for the primary and secondary outcomes will be conducted in the propensity score–matched study groups for the final study analyses when the target study size has been attained and results will be reported in the final study report. Analyses based on claims-identified cases, including outcomes that have unvalidated algorithms and outcomes that have

validated algorithms, will be presented. However, the primary comparative analyses for MCM will include only MCM outcomes that have been confirmed via medical record review or identified via published validated algorithms. Table 9 presents the measures of association planned for each outcome. Regression models will be used to compare pregnant women with migraine exposed to rimegepant during the exposure window with women in the primary comparator group and in the secondary comparator group. Point estimates and 95% CIs from crude analyses within the matched study groups will be presented. The number of pregnancies will be considered when determining which analyses can be conducted. The ability to match on propensity score is contingent on the available study size.

4.7.4 Missing Data

Using automated health care data, missing data for exposure, outcome, comorbidities, and comedications are expected to be minimal. In the presence of records for a given medical condition, it is assumed the medical condition is present, and in the absence of such records, it is assumed that the medical condition is absent. Otherwise, where relevant, the percentage of missing data will be reported (e.g., outcome data may be missing due to health plan disenrollment or infants not linked to maternal data, mother's geographic region of residence). Information on body mass index, smoking, and alcohol consumption is not recorded in health care claims databases. However, obesity will be ascertained through diagnosis codes for obesity–related disorders; alcohol consumption through diagnosis codes for alcohol abuse, dispensings of medications indicated for treatment of alcohol abuse, and alcoholism-related disorders; and smoking will be defined based on the use of smoking-cessation drugs and smoking-related diagnoses. It is acknowledged that this will underestimate the prevalence of obesity, alcoholism, and smoking.

4.7.5 Statistical Analyses

A summary of the analyses proposed for each outcome is presented in Table 9.

Prevalence of each outcome will be estimated, with the denominator being the number of units of analysis from which the cases arose and the numerator being the number of cases. For example, the prevalence of MCMs among the exposed will be the number of infants with MCMs identified in rimegepant-exposed live births with successful mother-infant linkage divided by the number of rimegepant-exposed live births with successful mother-infant linkage.

Analyses based on claims-identified cases, including outcomes that have unvalidated algorithms and outcomes that have validated algorithms, will be presented. However, the primary comparative analyses in the final report will only include outcomes that have been confirmed via medical record review or identified via published validated algorithms.

Table 9. Statistical Analyses of Study Outcomes

Outcome	Measure of Frequency (Objective 2)	Measure of Association (Regression Model) (Objective 3)	Timing of Outcome Ascertainment	Timing of Exposure Ascertainment	Unit of Analysis
Spontaneous abortions	Prevalence	Odds ratio (logistic regression)	Before week 20 of pregnancy	30 days before LMP up to the earliest of end of 20 weeks of pregnancy or end of pregnancy	Pregnancy
Fetal deaths/stillbirths	Prevalence	Odds ratio (logistic regression)	At or after week 20 of pregnancy	30 days before LMP or any time in pregnancy (i.e., before the time of fetal death)	Pregnancy
Elective terminations	Prevalence	Odds ratio (logistic regression)	Before week 20 of pregnancy	30 days before LMP up to the earliest of end of 20 weeks of pregnancy, or end of pregnancy if prior to end of 20 weeks	Pregnancy
Eclampsia/pre-eclampsia	Prevalence	Odds ratio (logistic regression)	At any time of pregnancy follow-up	30 days before LMP or any time in pregnancy	Pregnancy
Major congenital malformations	Prevalence	Odds ratio (logistic regression)	At birth or during infant follow-up	30 days before LMP up to and including first trimester of pregnancy	Fetuses (live births or others if the information is available for terminations or stillbirths) or live births
Small for gestational age	Prevalence	Odds ratio (logistic regression)	At birth	30 days before LMP or any time in pregnancy	Live births
Preterm births	Prevalence	Odds ratio (logistic regression)	At birth	30 days before LMP or any time in pregnancy, or at infant birth through end of first month after birth	Live births

LMP = first day of last menstrual period.

4.7.6 Subgroup Analyses

Possible stratifications (depending on counts) may include strata of maternal age (e.g., < 18 years, 18-34 years, ≥ 35 years), calendar year, and others (Table 10). Based on the observed pattern of rimegepant use, using information on the number of dispensed prescriptions,

days' supply and days between dispensings, rimegepant-exposed pregnancies will be grouped by whether women received rimegepant for acute treatment only, preventive treatment only, or for both, and subgroup analyses will be conducted for all study outcomes.

4.7.7 Sensitivity Analyses

Rimegepant is indicated for the acute treatment of migraine and for the preventive treatment of episodic migraine in adults. The recommended dose for the acute treatment is 75 mg taken orally, as needed, and the maximum dose in a 24-hour period is 75 mg. The recommended dose for the preventive treatment is 75 mg every other day. Based on information from claims for pharmacy dispensings, determining the time of exposure and whether the exposure occurred is uncertain. Pregnant patients may take medication during pregnancy that was prescribed and dispensed prior to the start of pregnancy. Even if medication was prescribed and dispensed during pregnancy, it is not possible to verify if the patient took the medication. Three sensitivity analyses are planned in relation to the definition of the exposure window and the timing of exposure (Table 10).

Moreover, several of the medications used for the treatment of acute migraine are available over the counter, and such use is not captured in health care databases based on administrative claims. Lack of data on over-the-counter medications is a limitation common to all observational studies using this type of data source. Data on the prevalence of use of over-the-counter medications for acute migraine collected in the Biohaven study BHV3000-402 will be used in the present study to inform a quantitative bias analysis; this bias analysis will provide information on the robustness of the study findings in relation with this source of exposure misclassification.

Additionally, it is unclear how many different medications will be included in the primary comparator group, whether acute or preventive treatments will be included, and whether stratification by type of medication (acute or preventive) will be possible.

Other sensitivity analysis are planned in relation to study outcome ascertainment. Table 10 presents the sensitivity analyses.

Table 10. Subgroup and Sensitivity Analyses

Topic	Application	Analysis
Exposure	All outcomes	Redefine the exposure window using the 75th percentile of the time between consecutive prescriptions to define the time window prior to the estimated LMP and through end of pregnancy
Exposure	All outcomes	Stratify by timing of exposure (by trimester of exposure, any time during pregnancy)
Exposure	All outcomes	Stratify by rimegepant patterns of use that correspond to acute treatment only, preventive treatment only, or both acute and preventive treatment
Exposure	All outcomes	Stratify by type of medication received in the primary comparator group (by medication category and by acute and preventive medications)
Exposure	Major congenital malformations	Restrict the rimegepant-exposed group to pregnant women with 2 or more dispensings in the 30-day period prior to the estimated conception and through pregnancy
Exposure	All outcomes	Quantitative bias analysis of exposure misclassification related to the use of over-the-counter medications to treat migraine
Outcomes	All outcomes	Stratify by maternal age at beginning of pregnancy (< 18 years, 18-34 years, ≥ 35 years)
Outcomes	Major congenital malformations	Restrict outcome to inpatient diagnoses

LMP = first day of last menstrual period.

4.8 Quality Control

Standard operating procedures or internal process guidance at the research center (Optum) and coordinating center (RTI-HS) will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, QC procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

For RTI-HS, an independent Office of Quality Assurance will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and IRB documentation. Such audits will be conducted by the Office of Quality Assurance according to established criteria in SOPs and other applicable procedures.

A quality assurance audit of this study may be conducted by the sponsor or the sponsor's designees.

Appropriate data storage and archiving procedures will be followed, with periodic backup of files to tape. Standard procedures will be in place to restore files in the event of a hardware or software failure at each research center.

The ORD contains data derived from claims submitted by providers and pharmacies to obtain payment for health care services rendered, data to track plan membership for premium billing, and provider data to track participating physicians who have contracts with health plans to provide services. The underlying administrative data are routinely captured, verified, automated, and de-identified. The data undergo regular audits and QC procedures by the insurer and are updated monthly. Although the health insurance claims data represent financial transactions and are not research records, the financial transactions related to the services provided create financial incentives to record them correctly and fully, so the billable medical services represented in the database are likely to be complete. The validity of this claims research database for epidemiologic research (as compared with data abstracted from medical records) has been established [80-83].

The study will be carried out according to the Optum Epidemiology group's internal SOPs, which are consistent with ISPE's Guidelines for Good Pharmacoepidemiology Practices. In particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

The validation of analytic work typically involves a combination of reviewing program logs and lists, independent coding, reviewing program processes and documentation to ensure that departmental SOPs are followed, and reconciling program code to ensure that populations and results are consistent with what is needed for the particular study. Individual programs are documented and revised as needed until sign-off by a validation analyst using a validation/programming log.

4.9 Limitations of the Research Methods

This study will be performed in existing administrative claims data, which are not primarily generated for research but for billing purposes. Many of the limitations of the study might arise from the potential for missing or misclassified study variables. Identification of study outcomes (spontaneous abortions, stillbirths, small-for-gestational-age births, or MCMs) may be challenging in automated health care databases using coded diagnoses. In addition, because of the US transition in 2015 from ICD-9 to ICD-10-CM coding for diagnosis in claims databases, there is a lack of validated algorithms using the new coding system for these outcomes. If applicable validation studies are published during the conduct of this study and show a claims-based algorithms with good performance, the study algorithms for the identification of study outcomes will be updated accordingly. However, the present study will include a validation of all study outcomes.

The diagnosis of migraine will be based on a claims-based algorithm used in previous studies. Although formal validation of this algorithm is not planned, an indirect validation process can be conducted by calculating the estimated prevalence of migraine as part of the process for identifying the study population using a claims-based algorithm adapted from those used recently in comparable populations and evaluating whether the estimated prevalence is in line with existing reports [22,36,48].

There is a risk of under-reporting of spontaneous abortions occurring during the first weeks of pregnancy if they were not captured through a claim. Only confirmed pregnancies or those requiring a medical visit will be captured through billing claims in the database. However, this risk of outcome misclassification would be nondifferential between the 3 study groups.

Left censoring may be a limitation for the ascertainment of baseline characteristics, such as prior comorbidities and past obstetrical history. The shorter the look-back period, the more likely it is that the baseline prevalence is underestimated, and this is most likely to occur for chronic conditions, which may have been recorded a long time before the study period begins. All the available information in the electronic record of the mother will be used to ascertain these variables to minimize left censoring. However, availability of information will depend on the time of enrollment of pregnant women in the health plans.

Prescription dispensing claims may not reflect actual exposure because only pharmacy dispensing information is captured, not actual patient use. Due to the type of medication under study (acute treatment of migraine or preventive treatment), the actual exposure will be uncertain because rimegepant and other medications indicated for the acute treatment of migraine are medications used on demand (e.g., during an episode of migraine). The complexity in migraine is that acute medication is taken "as needed" per the product label, and instructions for rimegepant are for use of a maximum dose of 75 mg (1 tablet) in a 24-hour period. For rimegepant, each dispensing constitutes 1 pack of 8 orally disintegrating tablets, and the estimated number of days for use is 30 days for acute treatment. For preventive treatment, given the recommended dose, it is anticipated that 2 packs will be used in a 30-day period. Rimegepant utilization will be assessed during the monitoring phase, the number of dispensings and the time interval between dispensings will help to determine if the 30-day window prior to the estimated LMP date for exposure ascertainment is adequate. In the current study, it was assumed that a patient is exposed at the time of the dispensing of the medication prescription. This might represent an overestimation of the true exposure. However, this overestimation would be nondifferential between triptans and other medications indicated for acute treatment of migraine and rimegepant users. The observed pattern of use of rimegepant based on information from dispensings will be used to identify treatment as acute only, preventive only, or both acute and preventive treatment. Sensitivity analyses with varying definitions of exposure and subgroup analyses by presumed acute and preventive use will be conducted. In addition, a patient survey in a sample of women drawn from the same source population as the study population is planned in order to collect information on how rimegepant and other medications for migraine are used. The survey aim is to validate the proposed approach to determine the exposure status in the current study.

Furthermore, some medications used for the treatment of migraine are available over the counter and are used to treat other forms of pain in addition to migraine. Although it is possible that over-the-counter use is mentioned in medical records for some patients, it is very plausible that most over-the-counter medication use is not recorded at all. Misclassification of over-the-counter drug use is common to all research using automated health care data. Efforts will be in place to identify exposure to these medications from other sources. The companion pregnancy registry study addressing postmarketing requirement PMR 3799-6 (Biohaven study BHV3000-402) will collect information on medications used for migraine, including prescription and over-the-counter medications, for both the exposed and comparator groups. Information will be collected

through a mobile app (much akin to the patient survey that FDA proposes) or other methods (e.g., paper, call center). Prevalence of use of over-the-counter medications for acute migraine from the companion pregnancy registry study will be used in the present study to inform a quantitative bias analysis; this bias analysis will provide information on the robustness of the study findings in relation with this source of exposure misclassification.

In addition, in studies evaluating the risk of exposure during pregnancies, the accurate identification of the beginning of pregnancy is crucial because some outcomes are occurring at specific time points of the pregnancy (e.g., during the first trimester). In the current study, the start of pregnancy will be estimated using the most appropriate and valid method [44,45,84].

Linkage of mothers and infants may not be completely successful in electronic health care claims databases. If the nonlinked mother-infant pairs had some differences compared with linked pairs, this may reflect a differential bias if the characteristics that are differential are associated with the exposure and the outcomes. However, this differential bias is not likely to be a factor in this study. The rate of successful mother-infant record linkage in Optum DAPI is reported to be approximately 85% for live births.

Sufficient uptake of rimegepant, a recently approved drug in the US, will be needed to conduct the study and to have conclusive results. A period of inclusion will be required to accrue enough exposed patients (currently expected to be 2020-2027). Annual interim analyses will inform the progress toward the target size. With a small study size, some study outcomes with very low incidence might not be detected, or estimates will be of limited precision.

Rimegepant is a recently approved medication compared with other more established migraine therapies such as triptans, used as comparators in this study. This study will include the time period when rimegepant was first approved, and thus, the use of rimegepant may change rapidly over time, and the specific profile and severity of early users may evolve when the drug becomes more established and its use increases [85]. Further, health plan coverage for rimegepant may require prior authorization or a “step-through” therapy (e.g., failure of triptans), so patients in the rimegepant-exposed group may have more severe forms of migraine than patients in the comparator groups.

Information on lifestyle variables (such as smoking; use of alcohol, cannabinoid-related products, or illicit drugs; and body mass index), as well as socioeconomic status, are not usually available in claims databases. Because these variables can be potential confounding factors or effect modifiers, indirect identification can be made through diagnosis codes for obesity and/or through dispensing drugs for smoking and alcohol disorders. In any case, the identification of these variables will likely be underestimated.

4.10 Other Aspects

Not applicable.

5 PROTECTION OF HUMAN SUBJECTS

This is a noninterventional study using secondary data collection and does not pose any risks for patients. All data collected in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Optum will apply for an independent ethics committee review according to local regulations; in addition, RTI-HS as the coordinating center will obtain approval or exemption from the RTI International (RTI-HS is a unit of the not-for-profit research organization RTI International) IRB.

5.1 RTI International

RTI International holds a Federal-Wide Assurance from the Department of Health and Human Services Office for Human Research Protections that allows the organization to review and approve human subject protocols through its IRB committees. RTI International currently has 3 IRB committees available to review research protocols. One IRB committee is constituted to review medical research and has 2 members who are medical doctors. These IRBs have been audited by the US FDA and are fully compliant with applicable regulatory requirements. RTI Health Solutions will obtain approval for the study from the RTI International IRB.

5.2 Optum

To ensure the quality and integrity of research, the conduct of this study will be governed by the Guidelines for Good Pharmacoepidemiology Practices issued by ISPE.

The research database is de-identified, and individual patient data are kept confidential and will not be shared with RTI-HS or Biohaven. All analyses will be performed in accordance with applicable laws and regulations. All study reports will contain only aggregated results and will not identify individual patients or physicians.

Optum research staff use de-identified data from the research database except in limited instances where applicable law allows the use of patient-identifiable data. For a subset of the patient population and with the appropriate approvals, Optum can augment the information derived from the research database with medical records, surveys, and other data sources.

5.2.1 Institutional Review Board Approval

Optum will prepare and submit the appropriate documents to a central IRB. Optum will communicate directly with the IRB to address any questions and/or provide any additional information in connection with the reviews. RTI Health Solutions and Biohaven will provide any necessary assistance or documents required for the IRB submission. Approval from an IRB for this study is not guaranteed. This study will be undertaken only after the study protocol and study documents have been approved and Optum is granted a waiver of authorization. The IRB will be asked to review and re-approve this study at least once a year.

5.2.2 Application for Approval of Medical Record Abstraction

An application will be submitted to an IRB for approval of the medical record abstraction process and documents. Documents to be submitted for review will likely include the following:

- Protocol
- Medical record procurement lists and abstraction form

Optum internal review and approval processes are also required. Optum will provide general study information and a copy of the IRB approval and waiver documents to the relevant data sources for approval to use such data in the study, which is not guaranteed.

6 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Based on current guidelines from ISPE [86] and the European Medicines Agency Guideline on Good Pharmacovigilance Practices: Module VI – Management and Reporting of Adverse Reactions to Medicinal Products [87], noninterventional studies, such as the one described in this protocol—conducted using medical chart reviews or electronic claims and health care records—do not require expedited reporting of adverse events/reactions. Based on the data planned for this study, no suspected adverse events/reactions are expected.

7 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The study protocol, study progress reports, and final study report will be included in regulatory communications in line with the risk management plan, Periodic Safety Update Reports, and other regulatory reporting requirements.

In its Guidelines for Good Pharmacoepidemiology Practices, ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" [86], e.g., results pertaining to the safety of a marketed medication. Study results may be published following guidelines, including those for authorship, established by the ICMJE [88]. When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed. Communication via appropriate scientific venues will be planned. The marketing authorization holder and the investigator will agree upon a publication policy.

8 OTHER GOOD RESEARCH PRACTICE

This study adheres to the Guidelines for Good Pharmacoepidemiology Practices [86] and has been designed in line with the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [89]. The ENCePP Checklist for Study Protocols [90] has been completed (see Annex 2).

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Annex 1. List of Stand-Alone Documents

None.

Annex 2. ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes," the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked, and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a noninterventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of noninterventional post-authorization safety studies). The checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the *Guideline for Good Pharmacovigilance Practices (GPP)*.

Study title:
Retrospective Cohort Study of Pregnancy Outcomes in Women Exposed to Rimegepant During Pregnancy

EU PAS Register® number:
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	1
1.1.2 End of data collection[2]	☒	☐	☐	1

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Progress report(s)	☒	☐	☐	1
1.1.4 Interim report(s)	☒	☐	☐	1
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	1
1.1.6 Final report of study results	☒	☐	☐	1

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	2
2.1.2 The objective(s) of the study?	☒	☐	☐	3
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	4.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	☒	☐	☐	4.1
3.2 Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	4.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	4.7.3
3.4 Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	4.7.3

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	☒	☐	☐	6

Comments:

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

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	4.3.1, 4.7.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	4.3.1, 4.7.1
5.3	Is exposure categorized according to time windows?	☒	☐	☐	4.3.1
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☒	☐	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	4.3.1, 4.7.1

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	4.3.2, 4.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQOL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	4.7.3
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	4.7.3
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	4.9

Comments:

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

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4.3, 4.4
	9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4.3, 4.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	4.3, 4.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	4.4
	9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	4.4
	9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, comedications, lifestyle)	☒	☐	☐	4.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	4.3
	9.3.2 Outcomes? (e.g., *International Classification of Diseases* (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3
	9.3.3 Covariates and other characteristics?	☒	☐	☐	4.3
9.4	Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	4.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	4.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	4.5
10.3 Are descriptive analyses included?	☒	☐	☐	4.7.2
10.4 Are stratified analyses included?	☒	☐	☐	4.7.6
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	4.7.3
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	4.7.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	4.7.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	4.6
11.2 Are methods of quality assurance described?	☒	☐	☐	4.6
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	4.6

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	4.9
12.1.2 Information bias?	☒	☐	☐	4.9

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	4.9
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	4.9

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	☒	☐	☐	5
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	5
13.3 Have data protection requirements been described?	☒	☐	☐	5

Comments:

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

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	☒	☐	☐	7
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	7

Comments:

Name of the main author of the protocol: Elena Rivero

Date: 08-Dec-2021

Signature: _____

Annex 3. Additional Information

Table 11. Medications for the Treatment of Migraine

Medication Category	Drugs[a]	Acute Migraine Treatment/ Preventive Treatment	Comments
Calcitonin gene–related peptide receptor antagonist	• Rimegepant • Ubrogepant	Acute treatment (rimegepant and ubrogepant) Preventive treatment (rimegepant)	With the exception of rimegepant, use of these medications is an exclusion criterion
NSAIDs	• Celecoxib • Diclofenac • Diflunisal • Etodolac • Fenoprofen • Flurbiprofen • Ibuprofen • Indomethacin • Ketoprofen • Ketorolac • Mefenamic acid • Meloxicam • Nabumetone • Naproxen • Oxaprozin • Piroxicam • Rofecoxib • Sulindac • Tolmetin • Valdecoxib	Acute treatment	Include parenteral forms and solid oral forms (tablets, pills; not liquid forms that are expected to be pediatric preparations) Over-the-counter medications will not be identified (study limitation) Source: FDA [91]
ASA	Acetyl salicylic acid		Over-the-counter medications will not be identified (study limitation)
Acetaminophen	Acetaminophen	Acute treatment	Over-the-counter medications will not be identified (study limitation)
Triptans	• Almotriptan • Eletriptan • Frovatriptan • Naratriptan • Rizatriptan • Sumatriptan • Zolmitriptan	Acute treatment	
Ditans	• Lasmiditan	Acute treatment	Use of these medications is an exclusion criterion
Ergots	• Dihydroergotamine • Ergotamine	Acute treatment	

Medication Category	Drugs[a]	Acute Migraine Treatment/ Preventive Treatment	Comments
Opioids	• Buprenorphine • Butorphanol • Codeine • Fentanyl • Hydrocodone • Dihydrocodeinone • Hydromorphone • Levorphanol • Meperidine • Methadone • Morphine • Nalbuphine • Oxycodone • Oxymorphone • Pentazocine • Propoxyphene • Tapentadol • Tramadol	Acute treatment	Include all parenteral and oral forms Over-the-counter medications will not be identified (study limitation) Source: National Institute on Drug Abuse [92]
Beta-blockers	• Atenolol • Bisoprolol • Carvedilol • Esmolol • Labetalol • Metoprolol • Nadolol • Pindolol • Propranolol • Sotalol • Timolol	Preventive treatment	Include all parenteral and oral forms
Anti-epileptics	• Clonazepam • Carbamazepine • Divalproex • Gabapentin • Levetiracetam • Lorazepam • Sodium valproate • Topiramate • Valproate • Valproic acid • Valproate semisodium	Preventive treatment	
Antidepressants	• Amitriptyline • Bupropion • Citalopram • Duloxetine • Fluoxetine • Nefazodone • Nortriptyline • Paroxetine • Sertraline • Trazodone • Venlafaxine	Preventive treatment	
Botulinum toxin	• OnabotulinumtoxinA	Preventive treatment	As use is topical, use for some FDA approved indications is not of interest for this study: overactive bladder, urinary incontinence, detrusor overactivity, spasticity, cervical dystonia, axillary hyperhidrosis, blepharospasm or strabismus [93]. Use for headache prophylaxis is of interest.
CGRP monoclonal antibodies	• Eptinezumab • Erenumab • Fremanezumab • Galcanezumab	Preventive treatment	Use of these medications is an exclusion criterion

Medication Category	Drugs[a]		Acute Migraine Treatment/ Preventive Treatment	Comments
Anti-nauseants	• Meclizine • Ondansetron • Granisetron	• Palonosetron • Rolapitant • Tolazamide		
Antipsychotics	• Risperidone • Paliperidone • Aripiprazole	• Quetiapine • Haloperidol • Olanzapine		
Steroid	• Corticosteroids	•		
Antihistamines	• Cyproheptadine			

CGRP = calcitonin gene–related peptide; FDA = Food and Drug Administration; NSAID = nonsteroidal anti-inflammatory drug.
[a] Include fixed-dose combinations of drugs available. As appropriate, drug list will be updated during the study.

Table 12. List of Teratogenic Medications

Drug Class/Generic Name	Half-life	Relevant Exposure Window
Androgens		
Methyltestosterone	2.5 to 3.5 h	First, second, and third trimesters
Testosterone	Per Google: Plasma half-life of testosterone ranges from 10 to 100 min. The cypionate and enanthate esters of testosterone have longer durations of action than testosterone. Cypionate half-life is about 8 days	First, second, and third trimesters
Mesterolone	12 to 13 h	Not in TERIS
Nandrolone	144 to 288 h	Not in TERIS
Oxandrolone	13.3 h	Not in TERIS
Prasterone	216 h	Not in TERIS
Fluoxymesterone	9.2 h	
Angiotensin II receptor antagonists		
Candesartan	9 h	First, second, and third trimesters
Eprosartan	5 to 9 h	First, second, and third trimesters
Irbesartan	11 to 15 h	First, second, and third trimesters
Losartan	2 h	First, second, and third trimesters
Olmesartan	13 h	First, second, and third trimesters
Tasosartan	Not available, but half-life of angiotensin II receptor antagonists range from 1 to 3 days	First, second, and third trimesters
Telmisartan	24 h	First, second, and third trimesters
Valsartan	6 h	First, second, and third trimesters
Angiotensin-converting enzyme inhibitors		
Benazepril	10 to 11 h	First, second, and third trimesters
Captopril	2 h	First, second, and third trimesters
Cilazapril	9 h	First, second, and third trimesters
Enalapril	11 h	First, second, and third trimesters
Fosinopril	11.5 to 14 h	First, second, and third trimesters
Lisinopril	12.6 h	First, second, and third trimesters
Moexipril	2 to 9 h	First, second, and third trimesters
Perindopril	0.8 to 1 h	First, second, and third trimesters
Quinapril	3 h	First, second, and third trimesters
Ramipril	13 to 17 h	First, second, and third trimesters

Drug Class/Generic Name	Half-life	Relevant Exposure Window
Trandolapril	6 h	First, second, and third trimesters
Antiarrhythmics		
Amiodarone	61 days	First, second, and third trimesters
Antibiotics		
Sulfamethoxazole/ Trimethoprim	8 to 10 h	3 months prior to conception and first trimester for MCMs and second trimester for preterm birth and low birth weight
Anticoagulants		
Acenocoumarol	8 to 11 h	First, second, and third trimesters
Dicumarol	5 to 28 h	At least 2 weeks prior to conception and first, second, and third trimesters
Phenprocoumon	4 to 6 days	First, second, and third trimesters
Warfarin	40 h	At least 2 weeks prior to conception and first, second, and third trimesters
Phenprocoumon	0.75 h	First trimester
Anticonvulsants		
Lamotrigine	Adult, 25.4 to 70.3 h (healthy volunteers); 12.6 to 58.8 h (epilepsy)	First, second, and third trimesters
Trimethadione/ Paramethadione	Paramethadione—12 to 24 h Trimethadione—11 to 16 h	First, second, and third trimesters
Valproic Acid, Valproate	4 to 16 h	Primarily first trimester, but MCMs have been associated with second and third trimester exposures
Carbamazepine	18 to 65 h	First, second, and third trimesters
Ethotoin	3 to 9 h	First, second, and third trimesters
Phenytoin, Fosphenytoin	15 min	First, second, and third trimesters
Primidone	10 h	First, second, and third trimesters
Topiramate	21 h	First, second, and third trimesters
Clonazepam	30 to 40 h	Unknown
Ethosuximide	17 to 56 hours	Unknown
Oxcarbazepine	Oxcarbazepine: immediate-release formulations, about 2 h; extended-release tablet, 7 to 11 h Active metabolite, 10–monohydroxy: 9 to 11 h	Unknown
Sulthiame	24 h	Not in TERIS
Vigabatrin	10.5 h	Unknown
Phenobarbital	70 to 140 h	First, second, and third trimesters

Drug Class/Generic Name	Half-life	Relevant Exposure Window
Methylphenobarbital	34 h	Not in TERIS
Antifungals		
Fluconazole	30 h	2 weeks before conception and first trimester
Flucytosine	2.4 to 4.8 hours	First trimester
Antineoplastics		
Aminopterin	12 to 24 h	First, second, and third trimesters
Asparaginase		
Axitinib		
Brentuximab vedotin		
Methotrexate	55 h	6 months prior to conception and first, second, and third trimesters
Crizotinib		
Cytarabine	1 to 3 h	First, second, and third trimesters
Daunorubicin	Per Google: The plasma half-life of daunorubicin averages 45 min in the initial phase and 18.5 h in the terminal phase. By 1 h after administration of daunorubicin, the predominant form of the drug in plasma is the metabolite daunorubicinol, which has as average terminal plasma half-life of 26.7 h	First, second, and third trimesters
Exemestane		
Mechlorethamine	11 h	First, second, and third trimesters
Mercaptopurine	47 min	Primarily first trimester, but other outcomes have been associated with exposures “during pregnancy”
Vinblastine	24.8 h	First, second, and third trimesters
Cyclophosphamide	3 to 12 h	First trimester
Altretamine	4.7-10.2 h	Unknown
Amsacrine	5 h	Unknown
Bevacizumab	480 h	Unknown
Bleomycin	2 h	Unknown
Bortezomib	40 to 193 h	Unknown
Busulfan	2.3 to 3.4 h	Not in TERIS
Capecitabine	0.75 h	Unknown
Carboplatin	24 h	Not in TERIS

Drug Class/Generic Name	Half-life	Relevant Exposure Window
Carmustine	IV, 22 min, 1.4 min (first phase), 17.8 min (second phase)	Unknown
Cetuximab	112 h	Unknown
Chlorambucil	1.5 h	Not in TERIS
Cisplatin	120 h	Not in TERIS
Cladribine	5.4 h	Not in TERIS
Clofarabine	5.2 h	Unknown
Dacarbazine	5 h	Unknown
Dactinomycin	36 h	Not in TERIS
Dasatinib	3 to 5 h	Unknown
Docetaxel	11.1 h	Unknown
Doxorubicin	20 to 48 h	Unknown
Epirubicin	31.1 h +/- 6 h to 35.3 h +/- 9 h	Not in TERIS
Erlotinib	36.2 h	Unknown
Estramustine	10 to 20 h	Not in TERIS
Etoposide	4 to 11 h	Unknown
Fludarabine	20 h	Unknown
Fluorouracil	8 to 20 min	Unknown
Gemcitabine	1.7 to 19.4 h	Not in TERIS
Hydroxycarbamide	2 to 4.5 h	Unknown
Idarubicin	20 to 22 h	Not in TERIS
Ifosfamide	15 h	Unknown
Imatinib	18 h	Unknown
Irinotecan	6 to 12 h	Unknown
Lapatinib	24 h	Unknown
Lomustine	16 to 48 h	Unknown
Melphalan	10 to 75 min	Unknown
Mitomycin	46 min	6 months before conception and first, second, and third trimesters
Mitoxantrone	23 to 215 h	Not in TERIS
Nelarabine	Adults: prodrug: 30 min; ara-G: 3 h	Unknown
Oxaliplatin	392 h	Unknown
Paclitaxel	13 to 52 h	Not in TERIS
Pemetrexed	3.5 h	Unknown

Drug Class/Generic Name	Half-life	Relevant Exposure Window
Pentostatin	5.7 h	Not in TERIS
Procarbazine	IV, approximately 10 min	Not in TERIS
Raltitrexed	260 h	Not in TERIS
Sorafenib	25 to 48 h	Unknown
Streptozocin	Systemic: 35 min unchanged drug; 40 h metabolites	Not in TERIS
Sunitinib	40 to 60 h	Unknown
Tegafur	6.7 to 11.3 h	Not in TERIS
Temozolomide	1.8 h	Unknown
Teniposide	5 h	Not in TERIS
Thioguanine	80 min	Not in TERIS
Thiotepa	1.4 to 3.7 h	Not in TERIS
Topotecan	2 to 3 h	Unknown
Vincristine	85 h	Unknown
Vindesine	2.9 h	Not in TERIS
Vinorelbine	27.7 to 43.6 h	Not in TERIS
Lenalidomide	3 h	Not in TERIS
Antithyroid		
Propylthiouracil	1 to 2 h	First and second trimesters
Methimazole	4.9 to 5.7 h	First, second, and third trimesters
Radioiodine	192 h	Unknown
Antivirals		
Ribavirin	12 days	6 months before conception and first, second, and third trimesters
Estrogens		
Diethylstilbestrol	Per Google: Once in the human body, diethylstilbestrol reaches peak concentration within 20 to 40 min, having a primary half-life of 3 to 6 h. It has a terminal half-life of 2 to 3 days due to entero-hepatic circulation, and is primarily excreted in urine	First, second, and third trimesters
Immunomodulatory agents		
Mycophenolate mofetil	16 h	First, second, and third trimesters
Thalidomide	5 to 7 h	1 month prior to conception and first, second, and third trimesters
Penicillamine	2 to 4 h	First, second, and third trimesters

Drug Class/Generic Name	Half-life	Relevant Exposure Window
Azathioprine	5 h	Primarily first trimester, but other outcomes have been associated with exposures "during pregnancy"
Leflunomide	432 to 456 h	Unknown
Mycophenolic acid	8 to 16 h	Primarily first trimester, but other outcomes have been associated with exposures "during pregnancy"
Mood stabilizer		
Lithium	24 h	First, second, and third trimesters
NSAIDs		
Indomethacin	4.5 h	Second and third trimesters; unlikely risk associated with first trimester exposure
Progestogens		
Medroxyprogesterone		First, second, and third trimesters
Prostaglandins analogue		
Misoprostol	20 to 40 min	1 month prior to conception and first, second, and third trimesters
Retinoids		
Alitretinoin	1 to 3 h	Unknown
Tretinoin	0.5 to 2 h	Unknown
Vitamin A	TERIS only notes "long half-life"	First, second, and third trimesters
Acitretin	50 to 60 h	2 years prior to stopping treatment and throughout pregnancy, especially first trimester
Etretinate	120 days to 3 years	10 years prior to stopping treatment and throughout pregnancy, especially first trimester
Isotretinoin	10 to 12 h	1 month prior to conception and first, second, and third trimesters
Tazarotene	18 h	Unknown
Retinol	2 to 9 h	12 months prior to conception and first trimester
Steroids		
Danazol	9.7 to 23.7 h	First, second, and third trimesters
Tetracyclines		
Demeclocycline	10 to 17 h	First, second, and third trimesters

Drug Class/Generic Name	Half-life	Relevant Exposure Window
Oxytetracycline	6 to 11 h	First, second, and third trimesters
Tetracycline	6 to 11 h	Second and third trimesters; limited data for first trimester exposure
Chlortetracycline	5.6 h	Unknown
Doxycycline	18 to 22 h	Unknown
Methacycline	14 to 22 h	Unknown
Minocycline	11 to 24.31 h	Unknown
Tigecycline	42.4 h	Unknown

IV = intravenous; MCM = major congenital malformation; NSAIDs = nonsteroidal anti-inflammatory drugs.
Sources: Eltonsy, Martin [62]; TERIS [94]; product labels, which are available at https://www.accessdata.fda.gov/scripts/cder/daf/.

Table 13. Characteristics of Women and Pregnancies

	Time Window of Ascertainment	Definition	Operational Form
Demographic and general characteristics			
Age	On date of LMP		Years
Duration of health plan enrollment	On date of LMP		Years
Year of pregnancy start	On date of LMP		Year
Year of pregnancy end	On date of pregnancy end		Year
Geographic region	On date of LMP		• Northeast • West • Midwest • South • Missing
Prior history of medical conditions			
Depression and bipolar disorders	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent
Anxiety and panic disorders	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent
Schizophrenia	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent
Epilepsy	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications[a]	Present/absent
Seizures	All available data within 6 months before and including LMP and during pregnancy	Defined through diagnosis codes and applicable medications[b]	Present/absent
Alcohol dependence	Available data within 6 months before and including LMP and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy
Substance abuse	Available data within 6 months before and including LMP and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy
Hyperlipidemia	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent

	Time Window of Ascertainment	Definition	Operational Form
Diabetes	All available data within 6 months before and including LMP	Defined through diagnosis codes not including gestational diabetes	Present/absent
Hypertension	All available data within 6 months before and including LMP	Defined through diagnosis codes, not including gestational hypertension	Present/absent
Malignancy	All available data before and including LMP	Defined through diagnosis codes	Present/absent
Thyroid disease	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Respiratory disease incl. asthma	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Liver disease	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Chronic kidney disease	All available data within 6 months before and including LMP	Defined through diagnosis codes and procedures	Present/absent
Obesity	All available data within 6 months before and including LMP	Defined through diagnosis codes and proxies (applicable medications and procedures)	Present/absent
Smoking	Available data within 6 months before and including LMP and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy
Cardiovascular diseases	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Cluster headache	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Migraine type	All available data before and including LMP and during pregnancy	Defined through diagnosis codes and applicable medications (see Section 9.2.1.2)	With aura, intractable With aura, not intractable Without aura, intractable Without aura, not intractable
Prior obstetric history			

	Time Window of Ascertainment	Definition	Operational Form
Gravidity	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Number of pregnancies (0, 1, 2 or more)
Parity	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Number of deliveries or C-sections (0, 1, 2 or more)
Spontaneous abortions	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Present/absent
Elective termination	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Present/absent
Live births with MCM	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm) and through diagnosis codes in linked infants	Present/absent
Stillbirth	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Present/absent
SGA	All available data within 3 years before current pregnancy	Defined through diagnosis codes	Present/absent
Gestational diabetes	All available data within 3 years before current pregnancy	Defined through diagnosis codes	Present/absent
Gestational hypertension	All available data within 3 years before current pregnancy	Defined through diagnosis codes	Present/absent

	Time Window of Ascertainment	Definition	Operational Form
Health care utilization			
Number of office visits	Available data within 6 months before LMP	Count of office visits	Number (0, 1, 2, ≥ 3)
Number of telemedicine encounters	Available data within 6 months before LMP	Count of telemedicine encounters	Number (0, 1, 2, ≥ 3)
Number of emergency department visits	Available data within 6 months before LMP	Count of emergency department visits	Number (0, 1, 2, ≥ 3)
Number of hospitalizations	Available data within 6 months before LMP	Count of hospitalizations	Number (0, 1, 2, ≥ 3)
Characteristics of current pregnancy			
Multiple pregnancy	During pregnancy	Defined through diagnosis codes	Present/absent
Gestational diabetes	During pregnancy	Defined through diagnosis codes	Present/absent
Gestational hypertension	During pregnancy	Defined through diagnosis codes	Present/absent
TORCH infections	During pregnancy	Defined through diagnosis codes	Present/absent
SARS-COV-2 infection	During pregnancy	Defined through diagnosis codes	Present/absent
Comedications			
Teratogens (medications listed in Table 12)	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, first trimester of pregnancy, or as indicated by relevant risk window
Cannabinoids	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Preventive cluster headache drugs	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Acute cluster headache drugs	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antidepressants	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antipsychotics	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy

	Time Window of Ascertainment	Definition	Operational Form
Oral antidiabetics	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Insulin	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antihypertensive medications	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Lipid-lowering drugs	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antithyroid medications	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antiplatelet agents	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Anticoagulants	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antiemetics and antinauseants	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Use of acute migraine medications (medications listed in Table 11): triptans, ergotamine derivatives, NSAIDs, acetaminophen, and opioids	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, and by trimester of pregnancy Number of users of each medication, number of different medications, number of dispensings, time (days) between dispensings
Use of preventive migraine drugs (medications listed in Table 11): topiramate, anti-epileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitor, and botulin toxin	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, and by trimester of pregnancy Number of users of each medication, number of different medications, number of dispensings, time (days) between dispensings

LMP = first day of last menstrual period; MCM = major congenital malformation; NSAID = nonsteroidal anti-inflammatory drug; SGA = small for gestational age; TORCH = toxoplasmosis, syphilis, varicella zoster, parvovirus B19, rubella, cytomegalovirus, herpes.

[a] Epilepsy will be identified based on at least 2 claims with diagnosis codes of epilepsy or status epilepticus on separate days and 1 or more dispensing for an antiepileptic drug. Validation studies of various algorithms have shown that the combination of diagnosis codes and claims for dispensing prescriptions for antiepileptic drugs have the highest positive predictive value [95].

[b] Isolated diagnosis codes for convulsions or epilepsy, or codes for convulsions or epilepsy that occur (1) only concurrently with codes for drug abuse or with pre-eclampsia/hypertension codes, (2) only around delivery, or (3) concurrent with other comorbidities that could lead to seizures will be defined as seizures [96].