# A Prospective, Registry-based, Observational Study to Assess Maternal, Fetal and Infant Outcomes Following Exposure to Rimegepant: The Migraine Observational Nurtec Pregnancy Registry (MONITOR)

## PROTOCOL BHV3000-402 V1.0

**Date: 18 Aug 2021**

# POST-AUTHORIZATION SAFETY STUDY (PASS) INFORMATION

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|---|---|
| Title | A Prospective, Registry-based, Observational Study to Assess Maternal, Fetal and Infant Outcomes Following Exposure to Rimegepant: The Migraine Observational Nurtec Pregnancy Registry (MONITOR) |
| Protocol version identifier | Version 1.0 |
| Date of last version | N/A |
| EU PAS register number | N/A |
| Active substance | Rimegepant; calcitonin gene-related peptide (CGRP) receptor antagonist |
| Medicinal product | Nurtec™ ODT (rimegepant) 75 mg orally disintegrating tablets |
| Product reference | BHV-3000 |
| Procedure number | N/A |
| Marketing authorization holder(s) | Biohaven Pharmaceuticals, Inc. |
| Joint PASS | No |
| Research question and objectives | The purpose of the study is to prospectively evaluate fetal, maternal, and infant outcomes through 12 months of age among women exposed to rimegepant during pregnancy, as well as in 2 comparison groups of women with and without migraine who are not exposed to rimegepant during pregnancy.<br>The primary objective is to compare the occurrence of major congenital malformations in the fetuses/infants of women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) to 1) an internal cohort of women with migraine not exposed to rimegepant before or during pregnancy and 2) an external cohort of pregnant women without migraine.<br>The secondary objectives are to describe the occurrence of adverse fetal outcomes, maternal pregnancy complications, infant outcomes at birth, and infant events of interest up to 1 year post-delivery in women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception), and to form comparisons to the same outcomes in 1) an internal cohort of women with migraine not exposed to rimegepant before or during |

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|---|---|
| | pregnancy and 2) an external cohort of pregnant women without migraine:<br>• Fetal outcomes (recognized spontaneous abortions, elective terminations, stillbirths, minor malformations)<br>• Maternal pregnancy complications (including but not limited to preeclampsia, eclampsia, gestational hypertension, gestational diabetes)<br>• Infant outcomes (including but not limited to preterm birth and small for gestational age)<br>• Other adverse events, including infant events of interest (including but not limited to postnatal growth deficiency and infant developmental delay up to 1 year of age) |
| Country(ies) of study | USA |
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# MARKETING AUTHORIZATION HOLDER

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# SPONSOR SIGNATUES

**Protocol Title:** A Prospective, Registry-based, Observational Study to Assess Maternal, Fetal and Infant Outcomes Following Exposure to Rimegepant: The Migraine Observational Nurtec Pregnancy Registry (MONITOR)

**Protocol Number:** BHV3000-402, V1.0

This protocol has been reviewed and approved by the Sponsor.

| Name and Title | Signature Approval | Date |
|---|---|---|
| Clinical Operations:<br>Andrea Ivans, MHS<br>Director, Clinical Operations | Beth Morris, Executive Director, Clinical Ops, Biohaven<br>Digitally signed by Beth Morris, Executive Director, Clinical Ops, Biohaven<br>Date: 2021.08.24 16:50:55 -04'00' | |
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| Regulatory Affairs:<br>Marianne Frost, MS<br>Vice President of Regulatory Affairs | Marianne Frost<br>Digitally signed by Marianne Frost<br>Reason: I am approving this document<br>Date: 2021.08.24 22:24:09 -04'00' | |

# SUMMARY OF CHANGES

| Change | Section(s) Affected | Summary |
|---|---|---|
| Original Protocol | Not Applicable | Not Applicable |

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# LIST OF ABBREVIATIONS

| Term | Definition |
|---|---|
| **BHV** | Biohaven Pharmaceuticals, Inc. |
| **CDC** | Centers for Disease Control and Prevention |
| **CDER** | Center for Drug Evaluation and Research |
| **CFR** | Code of Federal Regulations |
| **CGRP** | Calcitonin gene-related peptide |
| **CHD** | Congenital heart defect |
| **CI** | Confidence interval |
| **EDC** | Electronic data capture |
| **EDD** | Estimated date of delivery |
| **ENCePP** | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| **FDA** | Food and Drug Administration |
| **GPP** | Good Pharmacoepidemiology Practice |
| **HCP** | Healthcare provider |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **IHS** | International Headache Society |
| **IPW** | Inverse probability weighting |
| **IRB** | Institutional Review Board |
| **INTERGROWTH-21st** | International Fetal and Newborn Growth Consortium for the 21st Century |
| **LMP** | Last menstrual period |
| **MACDP** | Metropolitan Atlanta Congenital Defects Program |
| **MCM** | Major congenital malformation |
| **NDA** | New Drug Application |
| **NVSS** | National Vital Statistics System |
| **RCC** | Registry Coordinating Center |
| **SAB** | Spontaneous abortion |
| **SAC** | Scientific Advisory Committee |
| **SAE** | Serious adverse event |
| **SAP** | Statistical analysis plan |
| **SGA** | Small for gestational age |
| **SOP** | Standard operating procedure |
| **US** | United States |

# RESPONSIBLE PARTIES

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| Study Site | PPD<br>929 North Front Street<br>Wilmington, NC 28401 |
| MAH | Biohaven Pharmaceuticals, Inc. |
| MAH contact persons | Amy O'Donnell, JD, MD<br>Vice President, Head of Pharmacovigilance<br>Janet R. Hardy, PhD, MPH, MSc.<br>Executive Director and Head of Pharmacoepidemiology |

# ABSTRACT

Title: A Prospective, Registry-based, Observational Study to Assess Maternal, Fetal and Infant Outcomes Following Exposure to Rimegepant: The Migraine Observational Nurtec Pregnancy Registry (MONITOR)

- Rationale and background: Migraine prevalence is highest in women during childbearing years.[1] There is often a medical need for acute and/or preventive treatments of migraine during pregnancy, with treatment decisions based on clinical judgment of the benefits and the potential harms.[2] Generally, pregnant women are not included in clinical development programs. Further characterization of the population of pregnant women treated with rimegepant is warranted, as effects on the fetus after exposure in utero are unknown. Accordingly, this study has been mandated by the United States (US) Food and Drug Administration (FDA) to monitor pregnancy and infant outcomes.

- Research question and objectives: The purpose of the study is to prospectively evaluate fetal, maternal, and infant outcomes through 12 months of age in women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception), as well as in 2 comparison groups of women with and without migraine who are not exposed to rimegepant during pregnancy.

- The primary objective is to compare the occurrence of major congenital malformations (MCMs) in the fetuses/infants of women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) to 1) an internal cohort of women with migraine not exposed to rimegepant before or during pregnancy and 2) an external cohort of pregnant women without migraine.

  The secondary objectives are to compare the occurrence of adverse fetal outcomes, maternal pregnancy complications, infant outcomes at birth, and infant events of interest up to 1 year post-delivery in women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception), as well as in 1) an internal cohort of women with migraine not exposed to rimegepant before or during pregnancy and 2) an external cohort of pregnant women without migraine:

  - Fetal outcomes (recognized spontaneous abortions [SABs], elective terminations, stillbirths, minor malformations)

  - Maternal pregnancy complications (including but not limited to preeclampsia, eclampsia, gestational hypertension, gestational diabetes)

  - Infant outcomes (including but not limited to preterm birth and small for gestational age [SGA])

  - Other adverse events including infant events of interest (including but not limited to postnatal growth deficiency and infant developmental delay up to 1 year of age)

- Study design: This study is an observational, prospective, pregnancy exposure registry in line with the current FDA guidance for designing and implementing pregnancy exposure registries.[3]

- Population: The study population will include pregnant women within the US with migraine who were treated with rimegepant as part of routine care at any time during pregnancy or just prior to pregnancy (up to 3 days prior to conception), as well as 1) an internal cohort of women with migraine not exposed to rimegepant before or during pregnancy and 2) an external cohort of pregnant women without migraine.

  The minimum eligibility criteria required for enrollment are listed below.

  Inclusion:

  - Sufficient information to confirm eligibility
    - Pregnant women with migraine exposed to rimegepant: a diagnosis of migraine and at least 1 dose of rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception)
    - Pregnant women with migraine unexposed to rimegepant: a diagnosis of migraine and no exposure to rimegepant before or during pregnancy
  - Reporter (e.g., participant, maternal/infant healthcare provider [HCP]) contact information to allow for follow-up
  - Permission to contact the patient's and her infant's HCPs
  - Patient informed consent to participate

  Exclusion:

  - Women exposed to other calcitonin gene-related peptide (CGRP) antagonists (e.g., ubrogepant), CGRP monoclonal antibodies, or ditans (e.g., lasmiditan) at any time during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) will not be eligible for enrollment. If needed, this exclusion criterion may be revised to include these participants.

- Variables:

  *Exposure:* At least 1 dose of rimegepant at any time during pregnancy or just prior to pregnancy (up to 3 days prior to conception)

*Outcomes:*

- MCMs
- Pregnancy/fetal outcomes: recognized SABs, stillbirths, elective terminations, live births, minor congenital malformations
- Maternal pregnancy complications including but not limited to preeclampsia, eclampsia, gestational hypertension, gestational diabetes
- Infant outcomes at birth including but not limited to preterm birth, SGA
- Other adverse events including infant events of interest (including but not limited to postnatal growth deficiency and infant developmental delay up to 1 year of age)

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

- Study size*:* At present, the frequency of rimegepant exposure in pregnant women in addition to their willingness to enroll in a registry is unknown. We will, therefore, conduct the first 3 years from study initiation as a feasibility assessment, aiming to enroll a minimum of 100 pregnant women with rimegepant exposure and 100 untreated pregnant comparisons with migraine. All efforts will be made regarding registry awareness to facilitate the feasibility assessment's success. At the end of the 3 years and in consultation with the FDA, the success of the feasibility study will be evaluated. Based on success, the study will continue following the protocol timeline with the aim to enroll a minimum of 390 prospectively enrolled women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception), as well as 390 women with migraine not exposed to rimegepant before or during pregnancy. Each cohort of 390 is inclusive of its respective 100 feasibility study participants.

- Comparisons will be made to 2 groups consisting of:
  - 390 concurrently enrolled women with migraine unexposed to rimegepant: diagnosis of migraine and no exposure to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) (as defined in Section 3.4.1).
  - Pregnant women without migraine: No diagnosis of migraine from appropriate published US background outcome rates. The comparison population of the retrospective pregnancy outcomes study (New Drug Application [NDA] 212728, postmarketing requirement 3799-7, Biohaven study BHV3000-403) will serve as an additional resource for non-migraine comparison group outcome rates of major malformations, SABs, stillbirths, preterm births, and SGA.

- Data analysis: Demographic and baseline characteristics and prevalence rates of the outcomes of interest will be compared between the internal study cohorts: rimegepant-exposed participants with migraine (cohort #1) versus rimegepant-unexposed participants with migraine (cohort #2).

  Demographic and baseline characteristics will be summarized with descriptive statistics annually. Balance between cohorts will be assessed using standardized differences. These data will be presented before and after the data are balanced with the inverse probability weighting (IPW) method. In addition, within each cohort, those included in the analysis population will be compared with those excluded from the analysis population for being lost to follow-up, retrospectively enrolled, or exposed to teratogens during pregnancy.

  Formal quantitative comparisons of prevalence rates of the outcomes of interest will be conducted between the rimegepant-exposed and rimegepant-unexposed cohorts. For each outcome, if the number of events permits, results will be presented for both unadjusted and adjusted models. Summary statistics (relative risk) will be reported along with their 95% confidence intervals (CIs) and p-values. Adjusted methods will incorporate weights estimated using the IPW method to balance the cohorts with regard to observable covariates.

  Where sample size permits, subgroup analyses will be conducted that consider the timing and extent of exposure, the indication for migraine product (acute only, preventive only, or both), and maternal age group. Supplementary analyses will be conducted that include pregnant women who were excluded from the analysis population due to occurrence of the pregnancy outcome prior to enrollment (retrospectively enrolled participants) or exposure to a known teratogen during or prior to pregnancy (teratogen-exposed participants).

- Analyses will also be conducted to compare the prevalence rates of the outcomes of interest in the rimegepant-exposed participants in the analysis population with those of selected external comparators.

- Milestones: The study will be open for enrollment beginning in approximately July 2021. The estimated end of data collection is April 2034, and the final study report will be submitted by April 2035.

## AMENDMENTS AND UPDATES

Not Applicable.

## MILESTONES

| Milestone | Planned date |
|---|---|
| Start of data collection | Jul-2021 |
| End of data collection | Apr-2034 |
| Interim study report | Apr-2022 |
| Interim study report | Apr-2023 |
| Interim study report | Apr-2024 |
| Interim study report | Apr-2025 |
| Interim study report | Apr-2026 |
| Interim study report | Apr-2027 |
| Interim study report | Apr-2028 |
| Interim study report | Apr-2029 |
| Interim study report | Apr-2030 |
| Interim study report | Apr-2031 |
| Interim study report | Apr-2032 |
| Interim study report | Apr-2033 |
| Study completion | Apr-2034 |
| Final report of study results | Apr-2035 |

# 1 RATIONALE AND BACKGROUND

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.[4]

Migraine occurs more frequently in women than in men: a recent study reported the prevalence in males and females in the US adult population as 9.7% (95% CI, 9.1%-10.4%) and 20.7% (95% CI, 19.8%-21.6%), respectively.[5] The prevalence of migraine peaks in women of child-bearing age: 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.[1] In early pregnancy, some studies noted an approximate 40% of patients with any migraine experienced headache deterioration.[6] Alternatively, the frequency of migraines may decrease in pregnancy, particularly in the second and third trimester, and increase after delivery.[7] The cumulative prevalence of migraine throughout pregnancy was approximately 20% across 4 studies with over 34,000 patients.[8]

*Rimegepant and CGRP Receptor Antagonists*

Nurtec™ ODT (rimegepant or BHV-3000), a CGRP receptor antagonist developed by Biohaven Pharmaceuticals, Inc. (BHV), was approved by the US FDA in February 2020 for the acute treatment of migraine with or without aura in adults, and in May 2021 for preventive treatment of adults with episodic migraine. As background, CGRP is an endogenous 37 amino acid peptide contained within pain signaling nociceptive afferents, and is thought to play a causal role in migraine.[9,10] Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: 1) serum levels of CGRP are elevated during migraine,[11] 2) treatment with anti-migraine drugs returns CGRP levels to normal coincident with pain relief[11]; and 3) intravenous CGRP infusion produces lasting pain in non-migraineurs and migraineurs.[9,12] 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.[13] Note that the elimination half-life of rimegepant is approximately 11 hours in healthy (non-pregnant) subjects.

As of 03-Sep-2020, more than 7,200 subjects have participated in Phase 1 studies in healthy subjects, or Phase 2 and 3 studies in subjects with migraine. Among these subjects, more than 3,800 unique subjects have received the rimegepant clinical dose of 75 mg in Phase 2 and 3 studies, including more than 2,100 subjects in the 4 pivotal studies. More than 670 patients were exposed to rimegepant 75 mg for at least 12 months. Collectively, the data support a favorable overall benefit/risk profile and demonstrated broad and sustained efficacy for the comprehensive management of migraine with low risk of adverse events.

*Rimegepant and Pregnant Women*

There are no adequate data on the developmental risk associated with the use of rimegepant in pregnant women. In animal studies, oral administration of rimegepant at high doses (300 mg/kg/day; exposures over 200 times that observed in humans administered at the therapeutic dose of 75 mg) during organogenesis resulted in adverse effects on development in rats (decreased fetal body weight and increased incidence of fetal variations). These highest dose test exposures also resulted in maternal toxicity and were approximately 45 times the maximum recommended human dose (Nurtec PI).

As of 31-May-2020, there were a total of 32 women treated with rimegepant who reported pregnancies during the rimegepant clinical development program (in addition to 1 pregnancy reported in a partner assigned to rimegepant). Of these 32 treated women, 11 reported live births (in addition to 1 partner pregnancy), 6 reported SABs, 3 reported elective abortions, 4 had subsequently negative urine or serum pregnancy test results, and the 8 remaining women had unknown pregnancy outcomes and/or only an approximate due date was reported with no further follow-up information. There were 4 women assigned to placebo who reported pregnancies (in addition to 1 pregnancy reported in a partner assigned to placebo): 1 resulted in a live birth (in addition to 1 partner pregnancy), 2 had subsequent negative urine pregnancy test results, and 1 had an unknown pregnancy outcome. The rimegepant clinical development program remains ongoing, and pregnancy data will continue to be collected and monitored. One case on drug exposure during pregnancy was collected during postmarketing pharmacovigilance; however, the outcome of the pregnancy is not available, and no adverse event was reported.

Lastly, a study of breastfeeding women (lactation) with rimegepant (BHV3000-115) is underway with 6 women currently enrolled as of 05-Sep-2020.

*Migraine and Pregnancy Outcomes*

Migraine itself has been associated with an increased risk of some, but not all, adverse pregnancy outcomes. A recent population-based cohort study using Danish population registries identified 22,841 pregnancies among women with migraine and an age- and conception year-matched comparison cohort of 228,324 pregnancies among women without migraine.[14] Compared to the women without migraine, women with migraine, regardless of treatment type, were shown to have an increased risk of pregnancy-associated hypertension disorders and miscarriage, and an increased prevalence of low birth weight, preterm birth and cesarean delivery, but not for SGA and MCMs. Prevalence of any MCM was 3.1% in both women with and without migraine. Offspring prenatally exposed to maternal migraine had elevated risks of intensive care unit admission, hospitalization, dispensed prescriptions, respiratory distress syndrome, and febrile seizures, but not of death and cerebral palsy. The results suggested that migraine itself, rather than its treatment, is associated with adverse pregnancy and infant outcomes.[14]

Other investigators have similarly reported associations between migraine and gestational hypertension, preeclampsia,[15] low birth weight,[8,15,16,17] and preterm birth.[8,15] In earlier studies, women with migraine have been reported to be at increased risk of developing hypertensive disorders such as preeclampsia in pregnancy compared to women without migraine,[18,19] which is associated with an increased risk of low birth weight, preterm birth, and SGA infant.[19,20,21] In the migraine population, more severe migraine, defined by greater frequency and intensity, is associated with increased prevalence of cardiovascular comorbidity and comorbid affective disorders such as anxiety and depression.[22,23] In the US general population, the estimated background risk of MCMs and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. The estimated rates of MCMs (2.2% to 2.9%) and miscarriage (17%) among deliveries to women with migraine are similar to rates reported in women without migraine (Nurtec PI).

*Other Treatments for Migraine and Pregnancy Outcomes*

In the population-based cohort study using Danish population registries, migraine treatment type was categorized as untreated, acute treatment only, prophylactic treatment only, and both acute and prophylactic treatments. The study found no increased risk associated with migraine treatment (either acute, prophylactic, or both) for miscarriage, pregnancy-associated hypertension, adverse birth outcomes, including congenital malformations, or adverse neonatal or neurological outcomes in offspring,[14] including the outcomes of interest for this study.

Another challenge for evaluation of maternal, fetal, and infant outcomes is the established association of some specific prophylactic and acute antimigraine medications with congenital malformations and other study outcomes.[24] For example, valproic acid is teratogenic and contraindicated in pregnancy, topiramate has been associated with oral clefts at birth, and nonsteroidal anti-inflammatory drug use around the time of conception is associated with an increased risk of miscarriage.[25,26,27] These factors complicate the evaluation of maternal, fetal, and infant outcomes in migraine medication pregnancy exposure registries. Careful selection of comparison populations of women with migraine treated with preventive and/or other acute migraine medication is therefore needed when designing a study in order to accurately contextualize event rates.

A medical need for treatment of migraine during pregnancy may arise, with treatment decisions based on clinical judgment of the benefits and the potential harms.[2] Given the increased frequency of migraine in women of child-bearing age, it is anticipated that rimegepant exposure during pregnancy will occur in the post-authorization setting and thus further study is warranted. This prospective, registry-based, observational study to compare maternal, fetal, and infant outcomes of women with migraine exposed to rimegepant during pregnancy with 2 unexposed comparison populations is designed to satisfy the FDA post-marketing requirement for rimegepant (NDA 212728 Approval letter, 27-Feb-2020). The design and outcomes follow the FDA guidance on pregnancy safety studies,[3] and experience from other pregnancy studies, including pregnancy exposure registries.

# 2 STUDY OBJECTIVES AND OUTCOMES

## 2.1 Objectives

The purpose of the study is to prospectively evaluate fetal, maternal, and infant outcomes through 12 months of age in women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) (hereinafter referred to in the main text as "pregnant women with migraine exposed to rimegepant"), as well as in 2 comparison groups of women with and without migraine who are not exposed to rimegepant during pregnancy.

The primary objective is to compare the occurrence of MCMs in the fetuses/infants of women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) to 1) an internal comparator cohort of women with migraine not exposed to rimegepant before or during pregnancy (hereinafter referred to in the main text as "pregnant women with migraine unexposed to rimegepant") and 2) an external comparator cohort of pregnant women without migraine.

The secondary objectives are to compare the occurrence of the secondary outcomes (listed below) in women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) to 1) an internal comparator cohort of women with migraine not exposed to rimegepant before or during pregnancy and 2) an external comparator cohort of pregnant women without migraine.

## 2.2 Outcomes

The following lists the primary and secondary outcomes.

Primary outcome:

- MCMs

Secondary outcomes:

- Fetal outcomes (recognized SABs, elective terminations, stillbirths, minor congenital malformations)
- Maternal pregnancy complications (including but not limited to preeclampsia, eclampsia, gestational hypertension, gestational diabetes)
- Infant outcomes (including but not limited to preterm birth and SGA)
- Other adverse events including infant events of interest (including but not limited to postnatal growth deficiency and infant developmental delay up to 1 year of age)

# 3 RESEARCH METHODS

## 3.1 Study Design

This study is a prospective, observational, pregnancy exposure registry of US pregnant women with migraine exposed to rimegepant. The exposed cohort will be compared to: 1) an internal cohort of pregnant women with migraine unexposed to rimegepant and 2) an external cohort of pregnant women without migraine.

The study is designed according to the current FDA guidance for designing and implementing pregnancy exposure studies, including registries,[3] and is strictly observational.

## 3.2 Setting

### *3.2.1 Study Location*

This study is US-based.

### *3.2.2 Study Period*

The study will be open for enrollment beginning in approximately July 2021. The data collection process for each participant will begin at enrollment with data collection from both the participant and her HCP. For prospectively enrolled participants, follow-up with the maternal HCP will occur at the end of the second trimester (approximately 26 gestational weeks) and/or in the month of estimated date of delivery (EDD) for pregnancy outcome (delivery or early termination). The second trimester pregnancy follow-up may not be applicable for women who enroll late in pregnancy.

If a live birth is reported, the registry will conduct follow-up at 4 and 12 months after delivery with the infant's HCP. At approximately 4 months after delivery, infant data at 2 and 4 months of age will be collected; at approximately 12 months after delivery, infant data at 6 and 12 months of age will be collected.

An annual interim study report, reviewed by the Scientific Advisory Committee (SAC), will be submitted to the Center for Drug Evaluation and Research (CDER) beginning April 2022. The Interim Report summarizes the status and the cumulative data, current to the most recent annual data cutoff period. The estimated end of data collection is April 2034, and a final study report will be submitted by April 2035.

### *3.2.3 Study Participants*

The internal study population will include pregnant women of any age within the US with migraine who were treated with rimegepant as part of routine care at any time during pregnancy or just prior to pregnancy (up to 3 days prior to conception), as well as pregnant women with migraine not exposed to rimegepant before or during pregnancy. Eligible pregnant women may self-enroll or voluntarily be enrolled by their HCP. Enrollment should occur as early in pregnancy as possible.

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

Inclusion:

- Sufficient information to confirm eligibility
    - Pregnant women with migraine exposed to rimegepant (cohort #1): a diagnosis of migraine and at least 1 dose of rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception)
    - Pregnant women with migraine unexposed to rimegepant (cohort #2): a diagnosis of migraine and no exposure to rimegepant before or during pregnancy
- Reporter (e.g., participant, maternal/infant HCP) contact information to allow for follow-up
- Permission to contact the participant's and her infant's HCPs
- Patient informed consent to participate

Exclusion:

- Women exposed to other CGRP antagonists (e.g., ubrogepant), CGRP monoclonal antibodies, or ditans (e.g., lasmiditan) at any time during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) will not be eligible for enrollment.

  The reasons for this exclusion 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 potential payer restrictions (i.e., multiple branded therapies).

  At the end of the 3 years and in consultation with the FDA, the success of the feasibility study (Section 3.6) will be evaluated. As needed, strategies will be considered to support increased study enrollment, including exercising the option to revise the study exclusion criteria to include these participants.

### *3.2.4 Selection of Comparison Data*

The registry will include 2 comparison groups:

- Pregnant women with migraine unexposed to rimegepant cohort: migraine diagnosis and no exposure to rimegepant before or during the pregnancy period (as defined in Section 3.4.1)

- Pregnant women without migraine cohort: no migraine as determined from appropriate published US background outcome rates, and/or background rates to be obtained from the comparison population of the retrospective pregnancy outcomes study (NDA 212728, postmarketing requirement 3799-7, Biohaven study BHV3000-403), which will serve as an additional resource for non-migraine comparison group outcome rates of major malformations, SABs, stillbirths, preterm births, and SGA

This study will also use external published migraine and population-based data to provide context for any events observed in the pregnant women with migraine exposed to rimegepant cohort and the pregnant women with migraine unexposed to rimegepant cohort.

#### *3.2.4.1 Comparison Groups*

The registry will utilize 1) an internal cohort of women with migraine not exposed to rimegepant before or during pregnancy and 2) an external cohort of pregnant women without migraine as comparison groups. While women with migraine untreated with any therapy could be included in the pregnant women with migraine unexposed to rimegepant cohort, it should not be made up entirely of untreated women. Migraines are associated with some baseline pregnancy risks and comorbidities, and limiting to untreated comparisons may introduce bias among a cohort of women with less severe disease, or other fundamental population differences with potentially differential pregnancy outcomes.

For the internal comparator cohort of pregnant women with migraine unexposed to rimegepant: the reporting HCP for the pregnant women with migraine exposed to rimegepant will be asked to identify a pregnant woman with migraine unexposed to rimegepant as a comparison. Should the reporting physician not be able to identify an eligible woman, the comparison cohort could be supplemented with self-referred pregnant women who suffer from migraines or “friend-referrals” from participants.

For the external comparator group (pregnant women without migraine), the retrospective pregnancy outcomes study (NDA 212728, postmarketing requirement 3799-7, Biohaven study BHV3000-403) will serve as a resource for outcome rates of MCMs, SABs, stillbirths, preterm births, and SGA. The retrospective pregnancy outcomes study will be conducted in parallel to the registry and is specifically designed to complement the registry by monitoring these outcomes in a comparison group without migraine, providing annual updates in the interim reports until the study is completed. Additionally, appropriate published studies reporting representative rates will be selected to serve as comparisons.

#### *3.2.4.2 External Published Data*

The use of additional external studies will be considered to contextualize the findings of the registry. The published final results of the Sumatriptan, Naratriptan, Treximet Pregnancy Registry[28] represent a readily available external non-rimegepant, triptan-exposed historical pregnant migraine population. However, it is important to note that only MCMs apparent at birth were captured, as infants were not followed up to 1 year of age. In addition, while some pregnancy outcomes including SABs, fetal death/stillbirths, and elective terminations were collected, other outcomes of interest in this registry such as preeclampsia, gestational hypertension, preterm birth, SGA, and postnatal growth/development through 1 year of age were not collected.

Published results from the Metropolitan Atlanta Congenital Defects Program (MACDP) for congenital malformations, as well as published data for other outcomes of interest (e.g., the Centers for Disease Control and Prevention [CDC] National Vital Statistics System [NVSS] for the US prevalence of preterm birth)[29] can serve as supplemental sources for background rates. While the MACDP is considered to be the standard coding criteria for congenital malformation evaluation, there are well-known limitations such as geographic representation and participant demographics that are not ideally reflective of the whole US population. External sources are still useful to allow the assessment of generalizability of this study's findings and any other future study findings.

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

## 3.3 Participant Recruitment and Retention

### *3.3.1 Recruitment Strategy*

An active, targeted, multi-pronged recruitment campaign will be employed to recruit participants for the registry. The campaign will focus on:

- Pregnant women
- Patients with migraine
- Patients using rimegepant or other migraine therapies
- Obstetric HCPs
- HCPs who are likely to treat patients with migraine
- HCPs who are likely to prescribe rimegepant or other migraine therapies

Obstetric HCPs and HCPs who are likely to treat patients with migraine may be identified via HCP directories and/or professional associations. Pregnant women, patients with migraine, and patients using rimegepant or other migraine therapies may be identified through patient support groups, social media (e.g., Migraine Buddy), and external data sources (e.g., pharmacy claims or electronic medical records). The Sponsor's existing infrastructure for supporting stakeholders (e.g., the Biohaven medical information call center and patient support program) may be leveraged to identify HCPs who are known to prescribe rimegepant and pregnant women who are using rimegepant.

A multi-modal approach will be used to deliver registry education and recruitment materials to targeted HCPs and patients. This approach involves direct-to-HCP outreach as well as online and print advertising directed to both HCPs and patients. In addition, stakeholders may be identified and provided information regarding the registry via telephone through the Biohaven medical information call center, specialty pharmacies that dispense rimegepant, and the patient support program.

#### *3.3.1.1 Direct-to-HCP Outreach*

Direct-to-HCP outreach may be achieved by delivering recruitment materials to targeted HCPs via email, fax, and/or hardcopy mail. In addition, the Sponsor's representatives may provide registry education and recruitment materials to HCPs in person. HCPs will be asked to identify potential registry participants and encourage their participation by speaking to them about the registry and providing them with the patient-directed registry recruitment materials.

#### *3.3.1.2 Digital Advertising*

Information regarding the registry and the registry recruitment materials will also be available online. A registry-specific website will be developed, where recruitment materials will be available for download. This website will be accessible through the Nurtec consumer and HCP product websites and discoverable in any internet browser by performing a search related to pregnancy, Nurtec, and/or migraine. Information regarding the registry and/or a link to the registry website will also be available on the following websites:

- FDA listing of pregnancy registries on www.fda.gov, www.clinicaltrials.gov
- Society for Maternal-Fetal Medicine listing of registries
- Biohaven website
- PPD website

A web-based interface compatible with both computers and mobile devices will also be developed to improve information accessibility and enable broader participation. As deemed necessary, online advertisements on social media sites or other relevant websites (e.g., professional association websites or websites commonly visited by pregnant women or migraine patients) may be used to direct potential participants to the registry website.

The registry plans to partner with BabyCenter, a leading digital resource, to aid in recruitment. This resource is one of the most commonly used digital resources for pregnant women, reaching over 90% of first-time expectant women in the US and over 13 million monthly visitors. They are committed to providing pregnancy and parenting information worldwide via website and mobile application. The content is evidence-based and includes a wealth of information for parents and pregnant women, including tools to track pregnancy and baby's growth, answers to common questions regarding pregnancy and childbirth, and online communities to connect with other pregnant women, moms, and dads. Because it is already used by so many pregnant women, it is an ideal means to help recruit participants into the registry.

#### *3.3.1.3 Print Advertising*

Various print materials will also be used to provide information related to the registry and to facilitate recruitment. The Nurtec prescribing information will provide registry information, including contact information. Information related to the registry may also be directed to HCPs via announcements/publications in relevant professional journals/newsletters or presentations/exhibits at relevant professional meetings. As deemed necessary, print advertisements in newspapers or magazines with targeted patients among their readership may be used to direct potential participants to the registry, and recruitment materials may be distributed to locations commonly frequented by targeted patients (e.g., ultrasound clinics).

##### 3.3.1.3.1 Recruitment Materials

In addition to the registry information in the product label, educational materials designed to elicit interest in registry participation will be developed. All messaging will be aligned with the product label. Materials may include the following:

- An information sheet and/or brochure that will briefly describe the registry purpose and procedures, including the incentives for participation
- Information on how to access the registry web-based/mobile application
- Registration form and sample participant consent form
- Participant consent-to-contact card (this card enables the RCC to contact the potential participant and provide additional information about the registry)

### *3.3.2 Retention Strategy*

A retention strategy will be facilitated by engaging both the participant and HCP and seeks to minimize the reporting burden on these groups to the extent possible.

The registry staff will serve as the first and single point of communication for both registry participants and HCPs. The specialized staff, many of whom are obstetric nurses, have experience collecting data for observational studies from both patients and research-naive HCPs. They are experts at developing a rapport with HCPs and participants to facilitate data collection and build one-on-one relationships that will promote retention and reduce overall loss to

follow—up. To promote HCP engagement, status updates may be shared with HCPs through various means (i.e., email, newsletters, and the registry website). Materials provided will emphasize the mission of the registry to promote participant engagement and point participants to the website.

The registry will use streamlined data collection processes and simple, concise data collection forms that focus on endpoints of interest to reduce the burden of reporting. The registry will provide multiple options for communication and data submission (e.g., phone, fax, mail, email, website, web-based/mobile application) and a flexible follow-up schedule to enhance retention and maximize data reporting. The registry will also attempt to collect contact information of family members or friends in case the participant cannot be reached, which can further promote retention.

Finally, the registry will provide compensation to participants and their HCPs who serves as data reporters to the registry. Compensation will be sent to HCPs involved in pregnant women's care once pregnancy outcome data have been collected. Compensation will be sent to participants once pregnancy outcome data have been collected if fetal loss occurs or once 12-month infant outcome data have been collected if live birth occurs. Compensation will be sent to pediatric HCPs once 12-month infant outcome data have been collected.

## 3.4 Variables

### *3.4.1 Exposure of Interest*

Exposure to rimegepant is a condition for inclusion into the cohort of pregnant women with migraine exposed to rimegepant (cohort #1). In addition, pregnant women who are not exposed to rimegepant but who are exposed to other products for the treatment or prevention of migraine may be eligible for inclusion in the cohort of pregnant women unexposed to rimegepant (cohort #2). Finally, participants who are exposed to other CGRP antagonists (e.g., ubrogepant), CGRP monoclonal antibodies, or ditans (e.g., lasmiditan) will not be eligible for enrollment into either cohort. Appendix 1 provides a list of products for the treatment or prevention of migraine. This list of medications will be continually updated to reflect relevant newly approved medications.

Exposure is defined as bodily uptake of any dose of rimegepant or other migraine product at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (up to 5 product half-lives prior to conception). Due to the short elimination half-life of rimegepant (11 hours), the pre-pregnancy exposure period for rimegepant is relatively short; participants will be considered exposed during pregnancy if a dose is taken up to 3 days prior to the date of conception.

Information on prescribed dose, route, frequency, start/end dates, and indication/reason for use (for migraine products - acute only, preventive only, or both) will be collected from HCPs at enrollment, the end of the 2$^{nd}$ trimester, and pregnancy outcome. For acute and preventive migraine therapies (prescription and non-prescription), exposure during pregnancy will additionally be captured in real-time or near real-time from the participants via an exposure diary / migraine log. See Section 3.5.1 for more information.

Exposure will be further categorized by trimester of exposure; Section 3.5.3 provides information on the methods used to determine gestational age and trimester of exposure.

### *3.4.2 Disease of Interest*

A diagnosis of migraine (with or without aura) is a condition for inclusion into the internal study cohorts. For this study, the definition of migraine is consistent with the International Classification of Headache Disorders, 3rd Edition.[4] Disease information, including date of diagnosis and disease severity, will be collected from HCPs and/or participants.

### *3.4.3 Congenital Malformations, Pregnancy/Fetal Outcomes, Maternal Pregnancy Complications, Infant Outcomes, and Infant Events of Interest*

#### *3.4.3.1 Pregnancy Outcome*

Each **pregnancy outcome** will be reported as 1 of the following:

- Live birth: an infant born alive (any Apgar score > 0)
- Stillbirth: a fetal death occurring at ≥ 20 gestational weeks, or if gestational age is unknown, a fetus weighing ≥ 350 g
- Recognized SAB: fetal death or expulsion of products of conception occurring at < 20 gestational weeks. Terminology may include missed abortion, incomplete abortion, and inevitable abortion.
- Elective termination: voluntary interruption of pregnancy, including pregnancy termination that occurs electively, to preserve maternal health, or due to abnormalities

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

##### 3.4.3.1.1 Congenital Malformations

The study defines and codes congenital malformations with criteria specified by CDC MACDP[30]. A malformation may be described and classified by severity (e.g., major malformation), by origin (e.g., genetic, environmental exposure), and by organ system (e.g., urogenital system or congenital heart defects, malformations known as CHDs). An MCM is defined as any major structural or chromosomal defect detected in live-born infants, stillbirths/fetal losses ≥ 20 gestational weeks, and elective terminations of any gestational age.[30] This definition is consistent with, but not restricted to, the CDC MACDP definition.

To avoid misattribution of the malformation to the medication, MCMs not associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at < 36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses), will not be considered MCMs in the statistical analyses comparing MCM prevalence between the internal cohorts.[31] Given that the registry will also use CDC's MACDP as an external comparator, the registry will include cases of MCMs not associated with medication exposure in prevalence calculations for this comparison.

Transient malformations in term infants, whether occurring alone or with other malformations, will be reported in the study as certain transient malformations may be associated with maternal medication exposure in pregnancy and can vary by age of detection and/or age of resolution (e.g., CHDs).[32] Lastly, the MACDP only includes minor malformations if occurring in the presence of an MCM. However, as stated in the objectives, major and minor malformations are of interest for this study and both will be reported.

Live-born infants with only positional defects (malformations), infectious conditions, or with biochemical abnormalities will be classified and reported separately. The CDC MACDP project has different objectives and reporting needs than this project, and so a thoughtful adaptation of their guidelines is appropriate.

The registry will systematically collect information on major and minor structural malformations, transient malformations in term infants, and chromosomal defects that are apparent at birth and noted through infant age 1 year: congenital malformation(s) and details, if noted, type of congenital malformation(s) if applicable, attribution to drug therapy, and other factors that might have contributed to the outcome.

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

#### *3.4.3.2 Gestational Diabetes*

Defined as any degree of glucose intolerance with onset or first recognition during pregnancy[33].

#### *3.4.3.3 Gestational Hypertension*

Defined as high blood pressure occurring at >20 gestational weeks without signs of liver or kidney damage (e.g., proteinuria).[34]

#### *3.4.3.4 Preeclampsia*

Defined as high blood pressure and signs of liver or kidney damage (e.g., proteinuria) occurring at >20 gestational weeks.[34,35]

#### *3.4.3.5 Eclampsia*

Defined as seizures or coma in a pregnant woman with preeclampsia.[35]

#### *3.4.3.6 Preterm Birth*

Defined as an infant born at gestational age <37 weeks. As cases of preterm birth accrue and if appropriate, cases may be further classified by gestational age as: Extremely Preterm (<28 weeks), Very Preterm (28 to < 32 weeks), or Moderate to Late Preterm (32 to < 37 weeks).

#### *3.4.3.7 Small for Gestational Age*

Defined as birth weight < $10^{th}$ percentile for sex and gestational age. For the determination of SGA, the registry will utilize the sex-specific international growth reference standards from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) for those born between $24^{0/7}$ and $42^{6/7}$ gestational weeks.[36,37] The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multiethnic, diverse population, and have been specifically developed for modern research.

#### *3.4.3.8 Infant Events of Interest*

Include dates of follow-up evaluation, current age of infant, length, weight, head circumference, developmental milestones per the infant's HCP's assessment of normal, delayed, etc.

### *3.4.4 Other Variables*

See Section 3.5.1 for other variables that will be collected.

## 3.5 Data Sources

### *3.5.1 Overview of Data Collection Process*

The data collection process for each participant will begin at enrollment, and cumulative data throughout the pregnancy will be collected at 3 time points: at enrollment, at the end of the second trimester (approximately 26 gestational weeks), and at pregnancy outcome (live birth or fetal loss). For live-born infants, data from pediatric visits at 2, 4, 6, and 12 months of age will be collected at 2 time points: 4 months and 12 months after delivery. In addition, data related to migraine headaches and exposures to acute and preventive migraine therapies (prescription and non-prescription) during pregnancy will be collected in real-time or near real-time from enrolled pregnant women during pregnancy. It is expected that most participants will choose to complete the exposure log / migraine log via the registry's web-based/mobile application; however, alternate methods for completion will be available, including via telephone and paper data collection form that may be submitted to the registry via fax, email, or hardcopy mail. Weekly reminders to continuously complete the log will be sent to participants via the web-based/mobile application, email, and/or telephone.

Table 1 provides a summary of the data collection process, including the forms that will be used to collect the data, the timing for completion of each form, the potential reporters or sources of the data, and the types of data that will be collected. Sections 3.5.1.1, 3.5.1.2 and 3.5.1.3 provide additional details regarding the process and data being collected.

**Table 1. Summary of Data Collection Process**

| Data Collection Form | Data Sources/Reporters | Timing of Completion | Data Collected |
|---|---|---|---|
| ***Registration Form for Participants*** | Participant | Enrollment | • Registration information, including eligibility criteria<br>• Maternal demographic characteristics<br>• Disease information |
| ***Registration Form for HCPs*** | Obstetric HCP and prescriber, if needed | Enrollment | • Registration information, including eligibility criteria<br>• Maternal pre-pregnancy anthropometrics<br>• Maternal obstetrical history<br>• Family history of congenital malformations<br>• Disease information<br>• Baseline pregnancy information |
| ***Migraine Headache Log*** | Participant | In real-time or near real-time during pregnancy | • Disease information<br>• Maternal exposures to migraine therapies during pregnancy |
| ***Pregnancy Information Form*** | Obstetric HCP and prescriber, if needed | Enrollment, end of 2nd trimester[a], and EDD/pregnancy outcome[a] | • Ongoing pregnancy information<br>• Maternal exposures during pregnancy |
| ***Pregnancy Outcome Form*** | Obstetric HCP and pediatric HCP, if needed | EDD/pregnancy outcome | Pregnancy outcome information |
| ***Infant Outcomes Form*** | Pediatric HCP | 4 and 12 months after delivery | Infant outcome information at 2, 4, 6, and 12 months |
| ***Targeted Follow-up Form*** | Obstetric, pediatric, or other HCP | Any time after pregnancy outcome | Targeted follow-up information |

EDD = estimated date of delivery; HCP = healthcare provider.
[a] Obtain updated information since the previous contact.

#### *3.5.1.1 Information Collected at Enrollment*

After applicable informed consent is obtained from the eligible woman, the following information will be collected on the **Registration Form for Participants, Registration Form for Healthcare Providers, Migraine Headache Log,** and **Pregnancy Information Form**:

***Reporter Information***

*Collected from participant*

- Contact information for the participant, as well as alternate contact information, such as a permanent address and/or next of kin
- HCP reporter contact information (pediatric HCP information may be provided around time of EDD if unknown at enrollment)
- Request for Release of Medical Information Form(s) (form may be completed for pediatric HCP around time of EDD if unknown at enrollment)

***Registration Information***

*Collected from participant*

- Date of consent (enrollment)
- Recruitment source(s)
- Minimum data for assignment to a study cohort, including:
    - Country of residence
    - Pregnancy status
    - Diagnosis information
    - Exposure information
    - Prior enrollment status

*Collected from HCP(s) – obstetric and prescriber, if needed*

- Minimum data for assignment to a study cohort, including:
    - Pregnancy status
    - Diagnosis information

- Exposure information, including indication for prescription of rimegepant (acute only, preventive only, or both)

***Maternal Demographic Characteristics***

*Collected from participant*

- Maternal demographics

***Baseline Pregnancy Information***

*Collected from obstetric HCP*

- First day of last menstrual period (LMP)
- Method of conception

***Disease Information***

*Collected from participants and HCP(s) – obstetric and prescriber, if needed*

- Maternal history of migraine, including date of diagnosis

*Collected from participants*

- Characteristics of migraine, including measures of disease severity prior to pregnancy

*Collected from participants in real-time or near real-time during pregnancy*

- Dates of migraine headaches during pregnancy

***Maternal Pre-Pregnancy Anthropometrics***

*Collected from obstetric HCP; if not available from HCP, can be collected from participant*

- Pre-pregnancy anthropometrics (weight and height)

***Maternal Obstetrical History***

*Collected from obstetric HCP; if not available from HCP, can be collected from participant*

- Number of previous pregnancies (singleton or multiple)
- Outcome of all previous pregnancies
- Complications of previous pregnancies
- Characteristics of previous live births (preterm, SGA)

- History of offspring with congenital anomalies

***Family History of Congenital Malformations***

*Collected from obstetric HCP; if not available from HCP, can be collected from participant*

- Maternal and paternal history of congenital anomalies

***Maternal Exposures During Pregnancy***

*Collected from participants in real-time or near real-time during pregnancy*

- Daily recording of exposure to rimegepant or other acute and preventive migraine therapies (prescription and non-prescription), including name of product, dates of exposures, indication for use (acute only, preventive only, or both), and total dose taken on each date, if available

*Collected from HCP(s) – obstetric and prescriber, if needed*

- Exposure to drugs or biological products (including prescription and non-prescription drugs, dietary supplements, vaccines, and known teratogens), including indication/reason for use (for migraine products - acute only, preventive only, or both), dose, route, frequency, and dates/duration of exposure, if available

- Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available

***Ongoing Pregnancy Information***

*Collected from obstetric HCP; HCPs are asked only for updates to the data previously reported*

- Number of fetuses

- EDD and method of determination

- Prenatal tests performed, including type of test, date of test, and results/findings (e.g., congenital malformations)

- Concurrent maternal medical conditions, including but not limited to migraine, diabetes, hypertension, depression

- Concurrent pregnancy-related maternal medical conditions or pregnancy complications

- Note: Participants will be asked to complete an exposure log / migraine log beginning at enrollment and for the duration of pregnancy

#### *3.5.1.2 Information Collected at Pregnancy Follow-up*

At around the end of the second trimester, the HCP(s) will be asked to complete another ***Pregnancy Information Form***. For participants who enroll late in pregnancy, the end of second trimester follow-up might not be applicable. In the month of the EDD, the HCP(s) will be asked to complete another ***Pregnancy Information Form*** as well as the ***Pregnancy Outcome Form***. The participant is also contacted to provide authorization for medical release for the infant's pediatric HCP (if not previously obtained).

Follow-up at End of Second Trimester

***Disease Information***

*Collected from participants in real-time or near real-time during pregnancy*

- Dates of migraine headaches during pregnancy

***Maternal Exposures During Pregnancy***

*Collected from participants in real-time or near real-time during pregnancy*

- Daily recording of exposure to rimegepant or other acute and preventive migraine therapies (prescription and non-prescription), including name of product, dates of exposures, indication for use (acute only, preventive only, or both), and total dose taken on each date, if available

*Collected from HCP(s) – obstetric and prescriber, if needed*

- Exposure drugs or biological products (including prescription and non-prescription drugs, dietary supplements, vaccines, and known teratogens), including indication/reason for use (for migraine products - acute only, preventive only, or both), dose, route, frequency, and dates/duration of exposure, if available

- Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available

***Ongoing Pregnancy Information***

*Collected from obstetric HCP; HCPs are asked only for updates to the data previously reported*

- Number of fetuses

- EDD and method of determination

- Prenatal tests performed, including type of test, date of test, and results/findings (e.g., congenital malformations)

- Concurrent maternal medical conditions, including but not limited to migraine, diabetes, hypertension, depression

- Concurrent pregnancy-related maternal medical conditions or pregnancy complications

Follow-up at Pregnancy Outcome

***Disease Information***

*Collected from participants in real-time or near real-time during pregnancy*

- Dates of migraine headaches during pregnancy

***Maternal Exposures During Pregnancy***

*Collected from participants in real-time or near real-time during pregnancy*

- Daily recording of exposure to rimegepant or other acute and preventive migraine therapies (prescription and non-prescription), including name of product, dates of exposures, indication for use (acute only, preventive only, or both), and total dose taken on each date, if available

*Collected from HCP(s) – obstetric and prescriber, if needed*

- Exposure drugs or biological products (including prescription and non-prescription drugs, dietary supplements, vaccines, and known teratogens), including indication/reason for use (for migraine products - acute only, preventive only, or both), dose, route, frequency, and dates/duration of exposure, if available

- Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available

***Ongoing Pregnancy Information***

*Collected from obstetric HCP; HCPs are asked only for updates to the data previously reported*

- Number of fetuses

- EDD and method of determination

- Prenatal tests performed, including type of test, date of test, and results/findings (e.g., congenital malformations)

- Concurrent maternal medical conditions, including but not limited to migraine, diabetes, hypertension, depression

- Concurrent pregnancy-related maternal medical conditions or pregnancy complications

***Pregnancy Outcome Information***

*Collected from HCP(s) – obstetric and pediatric, if needed*

- Pregnancy outcome (live birth, stillbirth, SAB, elective termination)
- Date of outcome of pregnancy
- Gestational age at outcome
- Fetal/infant characteristics, including sex, birth weight, length, head circumference
- Route of delivery
- Delivery/birth complications, if any
- 5-minute Apgar score
- Congenital malformation(s) and potential contributing factors
- For a fetal loss (SAB, stillbirth), factors that may have had an impact on the fetal loss
- For elective termination, reason

#### 3.5.1.3 Information Collected at Pediatric Follow-up

***Timing of Pediatric Follow-up***

If a live birth occurs, the mother is asked to provide authorization for medical release for the infant's pediatric HCP to provide follow-up information. If authorization for medical release is obtained, the pediatric HCP will be asked to complete the ***Infant Outcomes Form*** at 4 and 12 months of age. At approximately 4 months after delivery, infant data at 2 and 4 months of age will be collected; at approximately 12 months after delivery, infant data at 6 and 12 months of age will be collected. To reduce recall bias, pediatric HCPs will be asked to provide data that are routinely documented in the infants' medical records at their visits at 2, 4, 6, and 12 months of age. This schedule follows the American Academy of Pediatrics' recommended infant well-child visit schedule.[38]

***Infant Outcome Information***

*Collected from pediatric HCP*

- Date of follow-up evaluation
- Current age of infant

- Current weight, length, head circumference of infant
- Developmental milestones per the HCP's assessment of normal, delayed, etc.
- Congenital malformation(s) and potential contributing factors
- Infant death, including date and cause of death

Targeted Follow-up After Report if an Event of Interest

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

***Targeted Follow-up Information***

*Collected from HCP(s) – obstetric and/or pediatric*

- Details of the congenital malformation or other event of interest
- Etiology
- Maternal infections/conditions of relevance to event
- Other information considered relevant by the HCP
- Specific questions requested by the birth defect evaluator (see Section 3.5.4)

### *3.5.2 Follow-up Process*

Attempts to Obtain the Follow-up Information

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. Three subsequent attempts, as necessary, will be made every 2 weeks via various modes of communication (e.g., phone, fax, email, mail). If no response is received from the HCP, additional attempts may occur at the next planned data collection time point (e.g., at pregnancy outcome). When appropriate, the participant will be asked to encourage her HCP to provide the missing data. A final communication will be sent indicating that the participant will be considered lost to follow-up if no further data are received. If this communication prompts a response from the HCP or the requested data are later received, the participant will no longer be considered lost to follow-up. If, at any point in the follow-up process, the participant withdraws consent or the HCP indicates that the participant is lost to follow-up, no further attempts will be made. The reason the participant was lost to follow-up (e.g., no response from HCP, no response from participant, or participant withdrawal of consent) will be documented.

Follow-up Process for Clarification of Information

For critical data points, if there are outstanding questions, discrepancies between forms, or missing data, the appropriate reporter will be contacted for clarification. Three subsequent attempts, as necessary, will be made every 2 weeks. If no further information is obtained, qualified registry staff or the principal investigator will make a logical determination on discrepant information based on the available data. All clarifications and/or changes will be documented and traceable.

### *3.5.3 Operational Exposure Definition*

When a pregnant woman self-enrolls in the study, she will be asked about treatment history with rimegepant. The pregnant woman will then be asked to provide a medical release that allows the RCC to confirm with the appropriate source any dates of specified pre-pregnancy or during pregnancy rimegepant treatment and ascertain the indication for prescription (i.e., acute only, preventive only, or both). Any additional rimegepant treatment and confirmation of indication will be captured by the participant in an exposure log / migraine log. Rimegepant exposure will be further categorized by earliest trimester of exposure.

For this study, gestational age will be estimated from the most reliable EDD as reported by the HCP or the pregnant woman. The following will be calculated based on EDD:

- First day of LMP, defined as $0^{0/7}$ gestational weeks, will be calculated as EDD minus 280 days (40 weeks)
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP
- Date of conception, defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks)

If the EDD is not available or never estimated, the first day of the LMP may be used to estimate gestational age. The second trimester will be considered to begin at Week 14 after LMP, and the third trimester at Week 28. If there is a discrepancy between gestational age calculated from LMP and reported gestational age, the HCP will be asked to verify the data.

### *3.5.4 Operational Outcome and Event Definition and Identification Process*

All pregnancy outcome and maternal/infant events of interest variables will be provided by the treating or obstetric HCP and the infant's pediatric HCP. In case no data on the pregnancy outcome can be obtained from the HCP, the pregnant woman will be asked to provide information on the pregnancy outcome. The HCP will be asked to describe any congenital malformations observed in the infant or fetus at birth and will also be asked to report the gestational age and birth weight, as described in the medical records. These last 2 variables will be used to calculate preterm birth (gestational age < 37 weeks at birth) and SGA (birth weight < 10th percentile for sex and gestational age) in live births.

A panel of 2 independent experts in clinical genetics, teratology, or neonatology will serve as birth defect evaluators and review all reported congenital malformations and classify them using the CDC's MACDP system as specified in Section 3.4.3. If there is a discrepancy, a third independent evaluator will independently review and code the case serving as tie breaker. The credentials of all birth defect evaluators will be verified prior to their participation in the study.

The method of assessment will be the same for both the exposed cohort and comparison cohort and the reviewers will be blinded to the exposure status.[3] This review includes identification of specific aspects of the case for further inquiry from the reporter(s), clarification and classification of the malformation(s) reported (in accordance with the classification conventions of the MACDP)[30] and a classification system, developed to facilitate the ability to generate potential signals.[39] The evaluator may assess a report as "pending further information" if more information is needed to determine the etiology of the malformation. However, if no further information is received despite repeated attempts, the evaluator can make an assessment based upon available information.

Once the exposure status blinding is broken following the review, the SAC (see Section 3.5.63.5.6) review includes definition of the potential relevance of timing of exposure to the event(s) reported – "temporality assessment." In addition, the review includes definition of the potential relevance of timing of exposure to the event(s) reported – "temporality assessment."

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

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

- Pending
- Development of this malformation and timing of exposure to the drug cannot rule out a possible association
- No temporal association
- Unable to assess
- Malformation with known cause; temporality may be irrelevant
- Pathogenesis of this malformation has yet to be defined specifically enough to assess temporality
- Not a malformation

### *3.5.5 Operational Variable(s) Definition*

As is indicated in Section 3.5, for women who self-enroll, maternal characteristics will be provided by the pregnant woman at study enrollment. After the woman provides consent and medical release for her HCP(s) to provide data, the therapeutic or obstetric HCP will provide prenatal data (LMP, EDD, and corrected EDD), prenatal test data (test, date of test, and result), obstetrical history (previous pregnancy outcomes, births with congenital malformations, and family history of congenital malformations), concomitant medical conditions, concomitant medications/vitamins/supplements, and alcohol, tobacco, marijuana, and illicit/recreational drug use. At pregnancy outcome, the obstetric HCP will be requested to provide pregnancy outcome data (live birth, stillbirth, SAB, elective termination), delivery data, and infant outcome data (including but not limited to gestational age, birth weight, length, head circumference, and sex). In case data on the pregnancy outcome cannot be obtained from the HCP, the woman will be asked to provide information on the pregnancy outcome. If not previously provided, the enrolled mother will be contacted to execute a Request for Release of Medical Information Form for the infant's HCP, and the HCP will be requested to provide information on the child at 4 and 12 months of age.

### *3.5.6 Scientific Advisory Committee*

A SAC will be established to oversee the scientific affairs of the study, including its ongoing monitoring. A charter for SAC activities, roles and responsibilities, and meeting frequency will be established following study initiation. The SAC will be composed of recognized experts including (but not limited to) the fields of teratology, epidemiology, maternal-fetal medicine, neonatology/pediatrics, and migraine treatment. The SAC will meet regularly to review the accumulated body of data from the study, including review of reported MCMs, which have been classified by independent birth defect evaluators, and other study outcomes, and to carry out any actions required, including review and interpretation of interim data analyses and reports and contribute to publications of study data. The SAC and birth defect evaluators will be independent of one another. The SAC may meet on ad hoc occasions if indicated. In addition to the above activities, the SAC will support the design and implementation of strategies to heighten awareness of the study.

## 3.6 Study Size

*Feasibility Assessment*

At present the frequency of rimegepant exposure in pregnant women and whether they will be willing to enroll in a registry is unknown. We will, therefore, conduct the first 3 years from study initiation as a feasibility assessment, aiming to enroll a minimum of 100 women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) and 100 women with migraine not exposed to rimegepant before or during pregnancy. All efforts will be made regarding registry awareness to facilitate the feasibility assessment's success. At the end of the 3 years and in consultation with the FDA, the success of the feasibility study will be evaluated. As needed, strategies will be considered to support increased study enrollment, including exercising the option to revise the study exclusion criteria

to include women exposed to other CGRP antagonists (e.g., ubrogepant), CGRP monoclonal antibodies, or ditans (e.g., lasmiditan) at any time during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception). Based on enrollment success, the study will continue following the protocol timeline and aim to enroll the sample as follows (sample size below is inclusive of the feasibility sample).

*Full Study*

The study aims to prospectively enroll a minimum of 390 women with migraine exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception), as well as an internal comparison cohort consisting of 390 women with migraine not exposed to rimegepant before or during pregnancy. The target sample size for the registry is based on the primary outcome, MCM, which is also the outcome with the most restrictive denominators and one of the lowest prevalence rates in the general population. If all are evaluable for potential MCMs (evaluable being those for whom pregnancy outcome and major/minor congenital malformation assessments are obtained), and assuming an approximate 3% overall population prevalence of MCM,[40] at $\alpha$=0.05, this sample size provides 80% power to detect a 2.5-fold increased risk for overall MCM. Most registry power calculations are performed for *overall* MCM to detect an increased risk between 2- and less than 3-fold.[41] A midpoint threshold of 2.5—fold increased risk was selected for this study. Assumptions for study calculations are consistent with those applied in the retrospective pregnancy outcomes study (NDA 212728, postmarketing requirement 3799-7, Biohaven study BHV3000-403).

Prospective enrollment can occur only after pregnancy is recognized but while the pregnancy is ongoing. Therefore, early pregnancy losses will not be captured, and a live birth rate higher than that of the general population would be expected. Research shows that approximately 90% of pregnancies enrolled in pregnancy exposure registries result in a live birth.[42,43] Assuming that 90% of prospectively enrolled pregnancies result in live births and 10% are lost to follow-up,[44] at $\alpha$=0.05, the study sample of 390 prospectively enrolled pregnant women in each internal cohort would result in 316 evaluable participants per cohort. Therefore, the study would have 80% power to detect a 2.7-fold increased risk of overall MCM (Table 2).

**Table 2. Sample Size and Power Estimates for Primary Outcome, MCM**

| Outcome | N per Cohort | Reference Rate | Relative Risk Detectable | Power[2] |
|---|---|---|---|---|
| MCM | 390 | 3%[40,41,45] | 2.5 | 80.6% |
| MCM | 316[1] | 3%[40,41,45] | 2.7 | 80% |

MCM = major congenital malformation; reference rate = prevalence rate of outcome in general population for pregnant women of any age.
[1] Assumes that 90% of prospectively enrolled pregnancies result in live births and 10% are lost to follow-up, resulting in 316 evaluable participants.
[2] Power calculations based on normal approximation, 2-tailed, $\alpha$=0.05.[46]

Additionally, Table 3 shows that, without any adjustments for multiple comparisons, the proposed sample size (390 pregnant women) will afford the study >80% power to detect a 2.5-fold increase in all other outcomes except eclampsia and stillbirth (for which the study will have < 20% power to detect a 2.5-fold increase).

**Table 3. Power Calculations**

| Outcome | Reference Rate | Power Estimate[1] |
|---|---|---|
| MCM[40,41,45] | 3% | 80.6% |
| Gestational diabetes[29] | 6.9% | >99.0% |
| Gestational hypertension[47] | 6.5% | >99.0% |
| Preeclampsia[48] | 3.40% | 85.5% |
| Eclampsia[47] | 0.3% | 2.7%[2] |
| SAB[49] | 13.4% | >99.0% |
| Stillbirth[50] | 0.596% | 12.6%[2] |
| Elective termination[51] | 18.6% | >99.0% |
| Preterm birth[29] | 8.47% | >99.0% |
| SGA* | 10.0% | >99.0% |
| Postnatal growth deficiency* | 10.0% | >99.0% |

MCM = major congenital malformation; reference rate = prevalence rate of outcome in general population for pregnant women of any age; SAB = spontaneous abortion; SGA = small for gestational age.
*By Definition
[1] Power calculations were conducted using nQuery and were based on normal approximation, 2-tailed, alpha 0.05.
[2] Fisher's exact test was used for power calculation.

## 3.7 Data Management

### *3.7.1 Data Processing*

Data for this prospective, observational safety study will be managed with an electronic data capture (EDC) platform that is compliant with 21 Code of Federal Regulations (CFR) Part 11. Variables described in the protocol under Section 3.3 will be solicited and entered in the EDC either directly by participants and/or their HCPs or indirectly by RCC personnel. Data provided by participants and/or their HCPs over the phone or on paper data collection forms, which can be submitted to the RCC via mail, email or fax, will be reviewed for correctness and completeness and entered into the database by RCC personnel.

### *3.7.2 Software and Hardware*

Data analyses will be performed using the statistical software program, SAS (version 9.4 or higher; SAS Institute, Cary, NC).

## 3.8 Methods of Analysis

Analyses will be conducted in accordance with the study objectives, statistical analysis plan (SAP), and applicable guidelines. Descriptive analyses for the primary and secondary study objectives will be performed for all data annually. Comparative analyses will be conducted for the final analysis.

Registry data will be summarized in tables and listings by study cohort, as appropriate. These data include maternal demographic characteristics and pre-pregnancy anthropometrics, pregnancy information, maternal obstetrical history, family history of congenital malformations, disease information, maternal exposures during pregnancy, pregnancy outcome information, and infant outcome information. For each continuous variable, the number of observations, median, mean, standard deviation, minimum, and maximum will be reported. For each categorical variable, the frequency and percentage in each category will be reported. The frequency and percentage of participants with missing data for each data point will be presented. Results will be rounded to one decimal place; therefore, percentages may not always add up to 100.

Pair-wise comparisons of demographic and baseline characteristics and prevalence rates of the outcomes of interest will be conducted between the study cohorts: pregnant women with migraine exposed to rimegepant (cohort #1) versus pregnant women with migraine unexposed to rimegepant (cohort #2).

The analysis population will include participants who are:

- Valid

  A valid participant is defined as a pregnant woman with sufficient data, submitted or confirmed by an HCP, for determining inclusion/exclusion into one of the study population cohorts. Participants who complete a ***Migraine Headache Log*** documenting their exposure to acute and preventive migraine therapies (prescription and non-prescription) during pregnancy will not be required to have HCP confirmation of exposure.

- Prospectively enrolled

  A prospectively enrolled participant is defined as a pregnant woman who enrolls in the registry prior to pregnancy outcome. A retrospectively enrolled participant is defined as a pregnant woman who enrols in the registry after the pregnancy outcome has occurred.

- Not considered lost to follow-up

  A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnant women without pregnancy outcome information will be considered lost to follow-up, and live-born infants without follow-up data after birth will be considered lost to follow-up.

For the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple gestation pregnancies will be excluded from the analysis population.

Comparisons will be conducted using the methods described below, and p-values and 95% CIs will be reported, as appropriate, to reflect statistical uncertainty. The study is not powered for multiple comparisons; thus, p-values associated with secondary outcomes will be nominal. Additional details are provided below and will be provided in the SAP.

### *3.8.1 Demographic and Baseline Characteristics*

Demographic and baseline characteristics will be summarized with descriptive statistics, and balance between cohorts will be assessed using standardized differences. These data will be presented before and after balancing using the IPW method (Section 3.8.2.43.8.2.4). In addition, within each cohort, those included in the analysis population will be compared with those excluded from the analysis population for being lost to follow-up or retrospectively enrolled.

### *3.8.2 Analysis of the Outcome Measures*

#### *3.8.2.1 Comparison With Internal Comparator Cohorts*

Formal quantitative comparisons of prevalence rates of the outcomes of interest will be conducted between the study cohorts. The prevalence rates of the outcomes of interest will be calculated as described in Section 3.8.2.3.

For each outcome, if the number of events permits, results will be presented for both unadjusted and adjusted models. Summary statistics (relative risk) will be reported along with their 95% CIs and p-values. For the primary outcome, a p-value $< 0.05$ will be considered statistically significant. Exact methods will be used to calculate crude (unadjusted) relative risks for binary outcomes, including MCM, minor congenital malformation, gestational diabetes, gestational hypertension, preeclampsia, eclampsia, SAB, stillbirth, elective termination, preterm birth, SGA, postnatal growth deficiency, and infant developmental delay.

Adjusted methods will incorporate weights estimated using the IPW method to balance the cohorts with regard to observable covariates (Section 3.8.2.4). For each binary outcome, a weighted generalized linear model using a binomial family and a log (relative risk) link will be employed to estimate an adjusted relative risk.

#### *3.8.2.2 Comparison With External Comparators*

Analyses will also be conducted to compare the prevalence rates of the outcomes of interest among rimegepant-exposed participants of the analysis population with those of selected external comparators (e.g., MACDP, NVSS), if available. Prevalence rates of the outcomes of interest will be calculated as described in Section 3.8.2.3. These registry prevalence rates will then be compared with those of selected external comparators using Exact methods. Prevalence rates will be reported along with their 95% CIs and p-values for the comparison.

#### *3.8.2.3 Calculation of Outcome Prevalence*

Prevalence rates of the outcomes of interest will be calculated according to the conventions described in Table 4. In general, the prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge and/or the methodology used by the external comparator. Prevalence is preferred over incidence when examining pregnancy outcomes, such as congenital malformations, because incidence cannot be reliably estimated given the complexities in the reproductive process.[52]

For most outcomes, the analysis population (denominator) will be the number of pregnant women with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the time point of interest, as appropriate; however, for some outcomes, the analysis population (denominator) will be restricted based on certain relevant factors:

- For MCM, prevalence in the rimegepant-exposed cohort will be calculated among the subset of women who are exposed during the first trimester.
- For MCM, prevalence will be calculated among live births for the primary analysis, and a secondary analysis will be conducted among live births and fetal losses.
- For preterm birth, SGA, and postnatal growth deficiency, prevalence will be calculated among singleton live births due to the higher risk of these outcomes in twins and higher order multiples.
- For live birth and infant outcomes (i.e., preterm birth, SGA, postnatal growth deficiency, and infant developmental delay), prevalence will be calculated among live births/infants without MCMs.
- For postnatal growth deficiency, infants born preterm or SGA will be excluded from the analysis population (denominator).
- For infant developmental delay, infants born preterm will be excluded from the analysis population (denominator).
- For SAB and preterm birth, prevalence will be calculated among the subset of women who are enrolled in the registry prior to 20 and 37 gestational weeks, respectively.

- For some outcomes, prevalence will be calculated at multiple time points. For example, postnatal growth deficiency and infant developmental delay will be assessed at 2, 4, 6, and 12 months of infant age. At each time point, prevalence will be calculated among infants with data available for the particular outcome at that time point.

For comparison with external comparators, the prevalence rates of the outcomes of interest among the rimegepant-exposed participants of the analysis population will be calculated according to the conventions used by the selected external comparators. For example, for comparison with MACDP, live births and stillbirths with MCMs, including MCMs not associated with medication exposure, will be included in the numerator, and the denominator will be the number of live births. The MACDP calculates rates by this convention, which increases sensitivity. Likewise, for comparisons with external cohort of pregnant women without migraine (from the retrospective pregnancy outcomes study), the conventions used to calculate outcome prevalence rates in the internal and external cohort will be aligned.

In addition, "crude" prevalence rates, without limitations and exclusions, may be conducted to avoid restricting the analysis population (denominator). For example, infants with MCM and/or infants born preterm may be included for the prevalence rate calculation of infant developmental delay.

## Table 4. Calculation of Outcome Prevalence

| Outcome | Numerator | Denominator |
|---|---|---|
| **Primary Outcome – MCM** | | |
| *Primary analysis: among live births with first trimester exposure (if applicable for cohort)* | Live births with confirmed MCMs (excluding MCMs not associated with medication exposure) among women with pregnancy outcome data and exposure during first trimester (if applicable) | Live births among women with pregnancy outcome data and, if applicable, exposure during first trimester |
| *Secondary analysis: among all pregnancy outcomes with first trimester exposure (if applicable for cohort)* | Live births and fetal losses with confirmed MCMs (excluding MCMs not associated with medication exposure) among women with pregnancy outcome data and, if applicable, exposure during first trimester | Live births and fetal losses among women with pregnancy outcome data and, if applicable, exposure during first trimester |
| *Secondary analysis: among live births with exposure at any time during pregnancy (if applicable for cohort)* | Live births with confirmed MCMs (excluding MCMs not associated with medication exposure) among women with pregnancy outcome data and, if applicable, exposure at any time during pregnancy | Live births among women with pregnancy outcome data and, if applicable, exposure at any time during pregnancy |
| *Secondary analysis: among all pregnancy outcomes with exposure at any time during pregnancy (if applicable for cohort)* | Live births and fetal losses with confirmed MCMs (excluding MCMs not associated with medication exposure) among women with pregnancy outcome data and, if | Live births and fetal losses among women with pregnancy outcome data and, if applicable, exposure at any time during pregnancy |

| Outcome | Numerator | Denominator |
|---|---|---|
| | applicable, exposure at any time during pregnancy | |
| *Comparison with external comparator (CDC MACDP)* | Live births and stillbirths with confirmed MCMs (including MCMs not associated with medication exposure) among women with pregnancy outcome data and exposure during the first trimester | Live births among women with pregnancy outcome data and exposure during the first trimester |
| **Secondary Outcomes** | | |
| Minor congenital malformations | Live births with minor congenital malformations among women with pregnancy outcome data | Live births among women with pregnancy outcome data |
| Gestational diabetes | | |
| *Primary analysis between internal cohorts* | Gestational diabetes among women with pregnancy outcome data | Women with pregnancy outcome data |
| *Comparison with external comparator (CDC NVSS)* | Gestational diabetes among live births | Live births among women with pregnancy outcome data |
| Gestational hypertension | | |
| *Primary analysis between internal cohorts* | Gestational hypertension among women with pregnancy outcome data | Women with pregnancy outcome data |
| *Comparison with external comparator*[47] | Gestational hypertension among live births | Live births among women with pregnancy outcome data |
| Preeclampsia | Preeclampsia among women with pregnancy outcome data | Women with pregnancy outcome data |
| Eclampsia | | |
| *Primary analysis between internal cohorts* | Eclampsia among women with pregnancy outcome data | Women with pregnancy outcome data |
| *Comparison with external comparator*[47] | Eclampsia among live births | Live births among women with pregnancy outcome data |
| SAB | SABs among women with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 20 gestational weeks | Women with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 20 gestational weeks |

| Outcome | Numerator | Denominator |
|---|---|---|
| Stillbirth | | |
| *Primary analysis between internal cohorts* | Stillbirths among women with pregnancy outcome data | Women with pregnancy outcome data |
| *Comparison with external comparator (CDC NVSS)* | Stillbirths among women with pregnancy outcome data | Live births and stillbirths among women with pregnancy outcome data |
| Elective termination | | |
| *Primary analysis between internal cohorts* | Elective terminations among women with pregnancy outcome data | Women with pregnancy outcome data |
| *Comparison with external comparator (CDC Abortion Surveillance System)* | Elective terminations among women with pregnancy outcome data | Live births among women with pregnancy outcome data |
| Preterm birth | Singleton preterm live births without MCMs among women with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 37 gestational weeks | Singleton live births without MCMs among women with pregnancy outcome data who are enrolled (and exposed, if applicable) prior to 37 gestational weeks |
| SGA | Singleton live births without MCMs who are SGA based on weight/length/head circumference among women with pregnancy outcome data | Singleton live births without MCMs with weight/length/head circumference data among women with pregnancy outcome data |
| Postnatal growth deficiency (at 2, 4, 6, and 12 months) | Singleton infants without MCMs who were not born preterm or SGA with postnatal growth deficiency based on weight/length/head circumference among infants with weight/length/head circumference data at the time point | Singleton infants without MCMs who were not born preterm or SGA with weight/length/head circumference data at the time point |
| Infant developmental delay (at 2, 4, 6, and 12 months) | Infants without MCMs who were not born preterm with developmental delay in a particular category among infants with developmental milestone data for the category at the time point | Infants without MCMs who were not born preterm with developmental milestone data for the category at the time point |

CDC = Centers for Disease Control and Prevention; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; NVSS = National Vital Statistics System; SAB = spontaneous abortion; SGA = small for gestational age.

#### *3.8.2.4 Adjustment for Covariates and Confounders*

Because of the real-world nature of the study, there is a high potential for imbalance between the cohorts with regard to observed covariates. To address this imbalance, adjusted analyses that employ the IPW method will be conducted. The IPW method is widely used in observational studies, and, unlike propensity score matching, the IPW method does not require a 1:1 match between participants in the 2 cohorts being compared.[53,54,55] The IPW approach assigns a weight to each participant based on observed covariates; the weight is equivalent to the inverse probability of the participant belonging in her assigned cohort. Weights will be estimated for each participant using logistic regression, then the weights will be incorporated into a regression model to balance the cohorts. When cohorts are far from being balanced, extreme weights can have an impact on the results. Stabilized weights are thus preferred and will be applied.

The final selection of covariates will depend primarily on data availability and clinical guidance, not data-driven methods. The list of covariates and confounders will be considered for each outcome separately. The final selection will be driven by clinical importance and by observed imbalances in the model. As the expected frequency of outcomes in the study is small, the number of potential covariates included in the model could be limited. Priority will be given to covariates that are possibly associated with the exposure and outcomes. In addition, a high rate of missing data for a covariate could make application of the IPW method more challenging, as weights can be estimated only for participants with known values.

##### 3.8.2.4.1 Potential Covariates and Confounders

In accordance with FDA and the Agency for Healthcare Research and Quality guidance,[3,56] the following potential covariates and confounders will be considered for inclusion in the logistic regression model used to derive participant weights and may also be included in multivariable analyses, as appropriate:

- Geographic region
- Calendar year at conception
- Maternal age at conception
- Maternal race
- Maternal ethnicity
- Proxies for maternal socioeconomic status, including maternal education, employment status, and income
- Maternal pre-pregnancy body mass index, calculated from pre-pregnancy weight and height
- Gestational age at registry enrollment

- Method of conception
- Number of fetuses
- Fetal/infant sex
- Concurrent maternal medical conditions, including thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders, hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (e.g., congenital uterine abnormalities)
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including gestational diabetes, gestational hypertension, preeclampsia, eclampsia, preterm labor, placental abruption, and incompetent cervix
- Number of previous pregnancies
- Previous pregnancy outcomes (SAB, stillbirth, elective termination, live birth)
- Previous pregnancy complications
- Characteristics of previous live births (preterm, SGA)
- Previous fetus/infant with congenital malformations (major and minor)
- Family history of congenital malformations (major and minor)
- Characteristics of migraine disease, including typical severity just prior to pregnancy (i.e., to establish baseline severity) and duration (i.e., time since diagnosis)
- Maternal exposure to other drugs or biological products, including prescription and non-prescription drugs, dietary supplements, and vaccines, during pregnancy and gestational age at exposure
- Maternal exposure to tobacco, alcohol, marijuana, and recreational or illicit drugs during pregnancy and timing of exposure

#### *3.8.2.5 Subgroup Analyses*

Where sample size permits, subgroup analyses will be conducted for all outcomes that consider:

- Timing of exposure (trimester of exposure)
    - For the analysis of MCM, the primary focus will be on exposure during the first trimester
- Extent of exposure (cumulative dose during pregnancy or relevant exposure window)
- Indication for use of rimegepant (acute only, preventive only, or both)
- Maternal age at conception (< 18 years, 18-34 years, and ≥ 35 years)

#### *3.8.2.6 Supplementary Analyses*

Supplementary analyses will be conducted that include pregnant women who were excluded from the analysis population due to:

- Occurrence of the pregnancy outcome prior to enrollment (retrospectively enrolled participants)

#### *3.8.2.7 Sensitivity Analyses*

Sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results. The following sensitivity analyses are planned:

- For the primary outcome, MCM, a sensitivity analysis will be conducted that excludes women exposed to known teratogens (e.g., valproic acid and topiramate) from the analysis population.

  Participants will be considered exposed during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to conception (up to 5 product half-lives prior to conception). A list of teratogens has been developed (Appendix 2) and will be continually updated based on the data available in the TERIS database of teratogenic agents and recent publications.[57,58,59]

- A sensitivity analysis will be conducted that applies a stricter definition of prospective enrollment. For this analysis, women who enroll in the registry prior to diagnostic prenatal testing will be considered prospectively enrolled, and women who enroll in the registry after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled. The outcomes of women who enroll prior to diagnostic prenatal testing will be compared with those of women who enrolled after diagnostic prenatal testing.

- For the primary outcome, MCM, a sensitivity analysis will be conducted that includes congenital malformations that are chromosomal or genetic.

- A maternal age sensitivity analysis will be conducted, stratified broadly by age group in years (e.g., younger than 18 years, 18-34 years, and 35 years or older).

Separate sensitivity analyses may also be conducted to assess the potential impact of missing data.

### *3.8.3 Missing Data*

For critical data points, missing values are expected to be minimal, thereby negating the need for imputation. As described in Section 3.5.2, the registry will make multiple attempts to obtain missing data for critical data points. The frequency and percentage of participants with missing data for each data point will be presented.

For start and end dates of medical conditions or exposures, if the month and year are known but the day is missing, then the day will be imputed for analyses: missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month. Listings will continue to present the day as missing.

If there is a high degree of missing covariate data, further imputation may be considered to minimize the loss of observations in the analysis.

## 3.9 Quality Control

### *3.9.1 Validation*

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

### *3.9.2 Record Retention*

The RCC will retain all study records required by the Sponsor and by the applicable regulations in a secure and safe facility for the duration of the study. The RCC will consult a Sponsor representative before disposal of any study records and must notify Sponsor of any change in the location, disposition, or custody of the study files. Electronic documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced will be retained by Sponsor for a period of 5 years in accordance with Good Pharmacoepidemiology Practice (GPP) guidelines. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements.

## 3.10 Limitations of the Research Methods

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

Those pregnancies that have reached EDD, but for which pregnancy outcome information was unobtainable, will be considered lost to follow-up. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in individual reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the losses to follow-up may have on the analysis. However, efforts at comparing some of the characteristics of each cohort may be conducted in an attempt to address this potential source of bias. Following the MACDP convention, calculation of MCM prevalence will exclude fetal losses (SABs, elective terminations, stillbirths, etc.) for which no MCMs have been diagnosed as they may introduce a classification bias. The percentage of these pregnancies consisting of potentially normal outcomes or MCMs is unknown. The data collection form attempts to obtain information on MCMs detected at the time of the outcome. However, the reporting physician may not know the condition of the aborted fetus.

Migraines are associated with some baseline pregnancy risks, including preeclampsia, and comorbidities, including cardiovascular comorbidity and affective disorders such as anxiety and depression.[22,23] It will be important to compare the pregnant women with migraine exposed to rimegepant and pregnant women with migraine unexposed to rimegepant rates for population differences that may potentially result in differential pregnancy outcomes and the introduction of bias. Additional available published external data sources in women with migraine, rates from the retrospective pregnancy outcomes study (NDA 212728, postmarketing requirement 3799-7, Biohaven study BHV3000-403; representing the pregnant women without migraine cohort), and the general population for estimates of selected outcomes will be evaluated to contextualize observed outcome occurrences in the registry.

An important potential limitation of this pregnancy registry is the possibility of lower than expected enrollment. This can result either because rimegepant is not being prescribed to, or used by, women who are or may become pregnant, or because exposed women are not being reported/enrolled into the registry. The feasibility study, planned for the initial 3 years of the study, will help provide an early evaluation of this possibility. If enrollment projections are not being met, it will be important to understand why and to identify additional strategies for increasing registry enrollment and/or identifying additional strategies for evaluating the safety of rimegepant exposure among pregnant women.

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

Potential biases related to the composition of the comparison cohort will need to be considered. The cohort of pregnant women with migraine unexposed to rimegepant may have been treated with other prescribed or over-the-counter migraine therapies (e.g. anti-epileptic medications including topiramate, tricyclic anti-depressants or beta-blockers) which can themselves be associated with adverse pregnancy outcomes, maternal pregnancy complications, and/or maternal comorbidities associated with adverse infant outcomes. The impact of type of migraine therapy in this cohort could be assessed in sensitivity analyses. Additionally, there may be differences in migraine severity between the cohort of pregnant women with migraine exposed to rimegepant and the comparison cohort of pregnant women with migraine unexposed to rimegepant. The impact of migraine itself will be taken into account by describing and, where possible, evaluating the relative occurrence of the study outcomes in the pregnant women with migraine exposed to rimegepant cohort and the pregnant women with migraine unexposed to rimegepant cohort. As possible, the relative impact of migraine will then be compared to findings from the retrospective pregnancy outcomes study (NDA 212728, postmarketing requirement 3799-7, Biohaven study BHV3000-403) comparison group (pregnant women without migraine) and with published external comparison data. If the number of women in the registry is small, baseline differences between the exposure cohorts may not be overcome, limiting the ability of the registry to provide meaningful conclusions.

# 4 PROTECTION OF HUMAN SUBJECTS

The Sponsor respects the participants' rights to privacy and will ensure the confidentiality of their medical information in accordance with applicable laws and regulations. Each participant's identity will be known only to the third-party contractor (i.e., PPD), the central registry site (principal investigator, medical monitor, and RCC), and the enrolling/participating individual (i.e., patient or HCP). At no time during the operation of the registry will the Sponsor have access to personal identifier information for any woman or any infant who has been enrolled in the registry, with the exception of date of birth for safety reporting purposes. The registry will assign all women and infants identification numbers, which will be used to identify registry participants and their infant offspring. The dataset used in each analysis of data from the registry will contain coded registry participant identifiers only for both the pregnant women and infants.

Each employee in the RCC is fully trained in the protection of human subjects and data privacy and follows established standard operating procedures (SOPs) that outline specifically how to maintain confidentially of and data protection for all registry participants. These SOPs also establish procedures should privacy be compromised in any way. The RCC staff must train and test on these privacy SOPs annually.

## 4.1 Exemption of Health Insurance Portability and Accountability Act Authorization

As a postmarketing safety reporting activity, this registry meets the following criteria and is therefore exempt from the US Health Insurance Portability and Accountability Act (HIPAA) authorization.

The CFR, in 45 CFR 164.512, states:

> (iii) A person subject to the jurisdiction of the Food and Drug Administration (FDA) with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity. Such purposes include:
>
> a. To collect or report adverse events (or similar activities with respect to food or dietary supplements), product defects or problems (including problems with the use or labeling of a product), or biological product deviations;
>
> b. To track FDA-regulated products;
>
> c. To enable product recalls, repairs, or replacement, or lookback (including locating and notifying individuals who have received products that have been recalled, withdrawn, or are the subject of lookback); or
>
> d. To conduct post marketing surveillance

To further clarify this issue, an article published by the Pregnancy Labeling Task Force, US FDA, states:

> The HIPAA Privacy Rule specifically permits the disclosure of protected health information by covered entities such as physicians or hospitals for public health purposes related to the quality, effectiveness and safety of FDA-regulated products to both the manufacturers and directly to the FDA. This includes collecting or reporting adverse events, tracking FDA-regulated products and conducting post-marketing surveillance to comply with requirements or at the direction of the FDA.[60]

## 4.2 Informed Consent

Informed consent will be obtained for each registry participant. Electronic consent will be available through the registry web-based/mobile application. Should participants prefer to enroll via phone, this registry qualifies for a waiver of documentation of informed consent. Adult participants will be given the option to provide verbal consent under the waiver of documentation of informed consent, or signed informed consent through the web-based/mobile application or via courier. Adults are defined as individuals who have attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US.

Minors are defined as individuals who have not attained the legal age for consenting to treatments, procedures, or clinical investigations under applicable law in various states within the US. The definitions of a minor and an emancipated minor vary by state within the US. This registry will follow applicable laws for the state in which the participant resides. If a minor requests participation in the registry and all eligibility criteria are met, the registry will obtain assent from the minor and signed written consent from a parent or guardian through the web-based/mobile application or via courier. Written consent from both parent(s) or both guardian(s) will be obtained in the US states in which this is required by local laws and regulations.

At the initial screening with potential participants, the registry web-based/mobile application or registry associate will obtain consent to collect basic information about the individual, such as age and state of residence, to determine whether the individual is a minor and to ensure that applicable local laws and regulations are followed.

### *4.2.1 Additional Safeguards for Children in Clinical Investigations*

Although this registry involves the collection of information on infants after birth, the registry protocol will be conducted in full consideration of 21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations (for FDA-regulated human subjects research). This registry will only ascertain maternal and infant information via maternal and pediatric HCPs, and no clinical specimens will be collected from the infants; therefore, data collected on infants of women in this pregnancy registry involves no greater than minimal risk to the infants. While the infants will be too young to provide assent, the registry protocol will require

permission from the mothers, and they will be asked to provide authorization for release of medical information from their infants' HCPs.

### *4.2.2 Electronic Informed Consent Process*

The website will contain information about the registry and will provide access to the study web-based/mobile application. Via the web-based/mobile application, the woman will register with her computer or mobile device using credentials (i.e., name, email address, and password).

Once the woman has registered, the application will automatically start the consent process. The application will present the contents of the consent in a scrollable window. The woman will review the document, and the application will present the following options: "Hold", "Disagree", and "Sign and Publish".

If the woman has questions during the consent process, she will be encouraged to stop the consenting process on the application via the "Hold" button and call the RCC, where study specialists will assist with any questions. The woman can resume completion of the consent process at any time. If the woman does not wish to provide consent, she will be directed to choose the "Disagree" option, and the process will stop. If the woman wishes to provide consent, she will be directed to choose "Sign and Publish".

The application will provide an option for the woman to view or email her completed consent form(s).

After the informed consent, the woman will complete the medical release form(s) and answer some basic medical information questions.

### *4.2.3 Waiver of Documentation of Informed Consent*

The following US regulations indicate that waiver of documentation of informed consent is appropriate for this registry.

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

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

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

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

**The research involves no more than minimal risk to the participants**. This is an observational study that involves no experimental intervention and poses no possibility of physical harm. The only potential risk is a breach of confidentiality, and the registry has well-established procedures in place to prevent any such breach of confidentiality. Extensive safeguards are in place to ensure that participants' privacy is protected:

a. An adequate plan is provided to protect the identifiers from improper use and disclosure.

b. An adequate plan is provided to remove the identifiers at the earliest opportunity.

c. Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

**The research involves no procedures for which written consent is normally required outside the research context.** Enrollment in this observational study will be strictly voluntary, and participants can withdraw their consent to participate at any time. The schedule of patient visits and all treatment regimens will be at the discretion of the treating HCP. Data submitted to the registry will be limited to data routinely collected and documented in the patient's medical record.

## 4.3 Regulatory and Ethical Compliance

This study was designed and shall be implemented and reported in accordance with the GPP guidelines,[61] with applicable local regulations and with the ethical principles established in the Declaration of Helsinki. The protocol will be submitted to the applicable regulatory authority and central IRB for approval prior to registry implementation. The protocol, waiver of documentation of informed consent, and waiver of informed consent will be reviewed and approved by an IRB before study implementation. A signed and dated statement that the protocol and waivers have been approved by the IRB will be given to the Sponsor before study initiation. Prior to study start, the investigator will sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol. If an inspection of the site is requested by a regulatory authority, the investigator must inform the Sponsor immediately that this request has been made.

# 5 MANAGEMENT AND REPORTING OF ADVERSE EVENTS

## 5.1 Primary Data Collection Study

The registry will actively solicit adverse events as defined in the study outcomes (Section 2.2). In addition to actively solicited SAEs, any maternal or infant death will be reported to Biohaven's pharmacovigilance vendor (PPD). All SAEs, solicited or unsolicited, will be reported within 1 business day of receipt. Biohaven will take ultimate responsibility for reporting all SAE data to the appropriate regulatory authorities within the required timeframe, as required by regulations. Serious adverse events reported in the cohort of pregnant women with migraine unexposed to rimegepant will be reported by the registry via MedWatch forms. Full details on how adverse events are defined, handled, and reported will be included in the safety and medical management plan.

# 6 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual interim and final study reports will be submitted to regulatory agencies.

The study will be registered in Clinicaltrials.gov, as well as in the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Registry.

Submissions to scientific congresses and/or to peer-reviewed journals are planned.

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# APPENDIX 1. LIST OF MIGRAINE THERAPIES

Table 5 provides a list of other migraine therapies. Please note, combination products of products already listed are not included.

### Table 5. List of Migraine Therapies

| Drug Class | Generic Name |
|---|---|
| Triptans | Almotriptan |
| | Eletriptan |
| | Frovatriptan |
| | Naratriptan |
| | Rizatriptan |
| | Sumatriptan |
| | Zolmotriptan |
| Anticonvulsants | Carbamazepine |
| | Clonazepam |
| | Diazepam |
| | Gabapentin |
| | Levetiracetam |
| | Lorazepam |
| | Topiramate |
| | Valproic acid |
| Pain therapies | Buprenorphine |
| | Butorphanol |
| | Dezocine |
| | Fentanyl |
| | Hydromorphone |
| | Levomethadyl |
| | Levorphanol |
| | Meperidine |
| | Methadone |
| | Morphine |
| | Nalbuphine |
| | Opium tincture |
| | Oxymorphone |

| Drug Class | Generic Name |
|---|---|
| | Oxycodone |
| | Pentazocine |
| | Sufentanil |
| | Tapentadol |
| | Tramadol |
| | Aspirin |
| | Acetaminophen |
| | Butalbital |
| | Hydroxycodeine |
| | Codeine |
| | Dihydrocodeine |
| | Drocode |
| | Ibuprofen |
| | Magnesium |
| | Calcium |
| | Meprobamate |
| | Dipyridamole |
| | Diphenhydramine |
| | Chlorpheniramine |
| | Pseudoephedrine |
| | Phenacetin |
| | Phenyltoloxamine |
| | Phenobarbital |
| | Salicylamide |
| | Carisoprodol |
| | Ethoheptazine |
| | Methocarbamol |
| | Opium |
| | Orphenadrine |
| | Propoxyphene |
| Antidepressants | Nefazadone |
| | Bupropion |
| | Amitriptyline |
| | Trazodone |

| Drug Class | Generic Name |
|---|---|
| | Nortriptyline |
| | Sertraline |
| | Fluoxetine |
| | Paroxetine |
| | Duloxetine |
| | Venlafaxine |
| Beta blockers | Atenolol |
| | Bisoprolol |
| | Carvedilol |
| | Esmolol |
| | Labetolol |
| | Metoprolol |
| | Nadolol |
| | Pindolol |
| | Propranolol |
| | Sotalol |
| | Timolol |
| Anti-nauseants | Meclizine |
| | Ondansetron |
| | Granisetron |
| | Palonosetron |
| | Rolapitant |
| | Tolazamide |
| Antipsychotics | Risperidone |
| | Paliperidone |
| | Aripiprazole |
| | Quetiapine |
| | Haloperidol |
| | Olanzapine |
| Steroid | Corticosteroids |
| Antihistamines | Cyproheptadine |
| Botox | Botulinum toxin type A |
| | Botulinum toxin type B |
| Ergotamine | Dihydroergotamine |

| Drug Class | Generic Name |
|---|---|
| | Ergotamine |
| CGRP inhibitors (with the exception of rimegepant, exposure to these agents is criteria for exclusion) | Fremanezumab |
| | Erenumab |
| | Galcanezumab |
| | Ubrogepant |
| | Rimegepant |
| Ditans (exposure to these agents is criteria for exclusion) | Lasmitidan |
| Complementary medications | Butterbur (petasites) |
| | Feverfew (MIG-99) |
| | Caffeine |

CGRP = calcitonin gene-related peptide.

# APPENDIX 2. LIST OF KNOWN TERATOGENS

Table 6 provides a list of known teratogens. This list has been developed and will be continually updated based on the data available in the TERIS database of teratogenic agents and recent publications[57,58,59]

## Table 6. List of Known Teratogens

| Drug Class | Generic Name | Half Life | Relevant Exposure Window |
|---|---|---|---|
| Androgen | Methyltestosterone | 2.5 to 3.5 h | 1st, 2nd, and 3rd 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. | 1st, 2nd, and 3rd 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 |
| Angiotensin II receptor antagonist | Candesartan | 9 h | 1st, 2nd, and 3rd trimesters |
| | Eprosaratan | 5 to 9 h | 1st, 2nd, and 3rd trimesters |
| | Irbesartan | 11 to 15 h | 1st, 2nd, and 3rd trimesters |
| | Losartan | 2 h | 1st, 2nd, and 3rd trimesters |
| | Olmesartan | 13 h | 1st, 2nd, and 3rd trimesters |
| | Tasosartan | Not available, but half-life of angiotensin II receptor antagonists range from 1 to 3 days | 1st, 2nd, and 3rd trimesters |
| | Telmisartan | 24 h | 1st, 2nd, and 3rd trimesters |
| | Valsartan | 6 h | 1st, 2nd, and 3rd trimesters |

| Drug Class | Generic Name | Half Life | Relevant Exposure Window |
|---|---|---|---|
| Angiotensin-converting enzyme inhibitors | Benazepril | 10 to 11 h | 1st, 2nd, and 3rd trimesters |
| | Captopril | 2 h | 1st, 2nd, and 3rd trimesters |
| | Cilazapril | 9 h | 1st, 2nd, and 3rd trimesters |
| | Enalapril | 11 h | 1st, 2nd, and 3rd trimesters |
| | Fosinopril | 11.5 to 14 h | 1st, 2nd, and 3rd trimesters |
| | Lisinopril | 12.6 h | 1st, 2nd, and 3rd trimesters |
| | Moexipril | 2 to 9 h | 1st, 2nd, and 3rd trimesters |
| | Perindopril | 0.8 to 1 h | 1st, 2nd, and 3rd trimesters |
| | Quinapril | 3 h | 1st, 2nd, and 3rd trimesters |
| | Ramipril | 13 to 17 h | 1st, 2nd, and 3rd trimesters |
| | Trandolapril | 6 h | 1st, 2nd, and 3rd trimesters |
| Antiarrhythmic | Amiodarone | 61 days | 1st, 2nd, and 3rd trimesters |
| Antibiotic | Sulfamethoxazole/ Trimethoprim | 8 to 10 h | 3 months prior to conception and 1st trimester for MCMs and 2nd trimester for preterm birth and low birth weight |
| Anticoagulant | Acenocoumarol | 8 to 11 h | 1st, 2nd, and 3rd trimesters |
| | Dicumarol | 5 to 28 h | At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters |
| | Phenprocoumon | 4 to 6 days | 1st, 2nd, and 3rd trimesters |
| | Warfarin | 40 h | At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters |
| | Fenprocoumon | 0.75 h | 1st trimester |
| Anticonvulsant | Lamotrigine | Adult, 25.4 to 70.3 h (healthy volunteers); 12.6 to 58.8 h (epilepsy) | 1st, 2nd, and 3rd trimesters |
| | Trimethadione/ Paramethadione | Paramethadione—12 to 24 h<br>Trimethadione—11 to 16 h | 1st, 2nd, and 3rd trimesters |
| | Valproic Acid/Valproate | 4 to 16 h | Primarily 1st trimester, but MCMs have been associated with 2nd and 3rd trimester exposures. |
| | Carbamazepine | 18 to 65 h | 1st, 2nd, and 3rd trimesters |
| | Ethotoin | 3 to 9 h | 1st, 2nd, and 3rd trimesters |

| Drug Class | Generic Name | Half Life | Relevant Exposure Window |
|---|---|---|---|
| | Phenytoin/Fosphenytoin | 15 min | 1st, 2nd, and 3rd trimesters |
| | Primidone | 10 h | 1st, 2nd, and 3rd trimesters |
| | Topiramate | 21 h | 1st, 2nd, and 3rd 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<br>Active metabolite, 10–monohydroxy: 9 to 11 h | Unknown |
| | Sultiam | 24 h | Not in TERIS |
| | Vigabatrin | 10.5 h | Unknown |
| | Phenobarbital | 70 to 140 h | 1st, 2nd, and 3rd trimesters |
| | Methylfenobarbital | 34 h | Not in TERIS |
| Antifungal | Fluconazole | 30 h | 2 weeks before conception and 1st trimester |
| Antineoplastic | Aminopterin | 12 to 24 h | 1st, 2nd, and 3rd trimesters |
| | Methotrexate | 55 h | 6 months prior to conception and 1st, 2nd, and 3rd trimesters |
| | Cytarabine | 1 to 3 h | 1st, 2nd, and 3rd 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 | 1st, 2nd, and 3rd trimesters |
| | Mechlorethamine | 11 h | 1st, 2nd, and 3rd trimesters |
| | Mercaptopurine | 47 min | Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy" |
| | Vinblastine | 24.8 h | 1st, 2nd, and 3rd trimesters |

| Drug Class | Generic Name | Half Life | Relevant Exposure Window |
|---|---|---|---|
| | Cyclophosphamide | 3 to 12 h | 1st 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 |
| | Carmustine | IV, 22 min, 1.4 min (1st phase), 17.8 min (2nd 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 |

| Drug Class | Generic Name | Half Life | Relevant Exposure Window |
|---|---|---|---|
| | Irinotecan | 6 to 12 h | Unknown |
| | Lapatinib | 24 h | Unknown |
| | Lomustine | 16 to 48 h | Unknown |
| | Melphalan | 10 to 75 min | Unknown |
| | Mitocycine (misspelled - mitomycine) | 46 min | Not in TERIS |
| | 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 |
| | 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 |
| | Streptozocine (misspelled - streptozotocin) | 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 | 1st and 2nd trimesters |
| | Methimazole | 4.9 to 5.7 h | 1st, 2nd, and 3rd trimesters |
| | Radioiodine | 192 h | Unknown |
| Estrogen | Diethylstilbestrol | Per Google: Once in the human body, DES reaches | 1st, 2nd, and 3rd trimesters |

| Drug Class | Generic Name | Half Life | Relevant Exposure Window |
|---|---|---|---|
| | | 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 | |
| Immunomodulatory agent | Mycophenolate mofetil | 16 h | 1st, 2nd, and 3rd trimesters |
| | Thalidomide | 5 to 7 h | 1 month prior to conception and 1st, 2nd, and 3rd trimesters |
| | Penicillamine | 2 to 4 h | 1st, 2nd, and 3rd trimesters |
| | Azathioprine | 5 h | Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy" |
| | Leflunomide | 432 to 456 h | Unknown |
| | Mycophenolic acid | 8 to 16 h | Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy" |
| Mood stabilizer | Lithium | 24 h | 1st, 2nd, and 3rd trimesters |
| Nonsteroidal anti-inflammatory drug | Indomethacin | 4.5 h | 2nd and 3rd trimesters; unlikely risk associated with 1st trimester exposure |
| Prostaglandins analogue | Misoprostol | 20 to 40 min | 1 month prior to conception and 1st, 2nd, and 3rd trimesters |
| Retinoid | Alitretinoin | 1 to 3 h | Unknown |
| | Tretinoin | 0.5 to 2 h | Unknown |
| | Vitamin A | TERIS only notes "long half-life"; 75 days per Google search | 1st, 2nd, and 3rd trimesters |
| | Acitretin | 50 to 60 h | 2 years prior to stopping treatment and throughout pregnancy, especially 1st trimester |
| | Etretinate | 120 days to 3 years | 10 years prior to stopping treatment and throughout pregnancy, especially 1st trimester |
| | Isotretinoin | 10 to 12 h | 1 month prior to conception and 1st, 2nd, |

| Drug Class | Generic Name | Half Life | Relevant Exposure Window |
|---|---|---|---|
| | | | and 3rd trimesters |
| | Tazarotene | 18 h | Unknown |
| | Retinol | 2 to 9 h | 12 months prior to conception and 1st trimester |
| Steroid | Danazol | 9.7 to 23.7 h | 1st, 2nd, and 3rd trimesters |
| Tetracycline antibiotic | Demeclocycline | 10 to 17 h | 1st, 2nd, and 3rd trimesters |
| | Oxytetracycline | 6 to 11 h | 1st, 2nd, and 3rd trimesters |
| | Tetracycline | 6 to 11 h | 2nd and 3rd trimesters; limited data for 1st 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 |