NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

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	C4951005 (formerly BHV3000-402)
Protocol version identifier	3.0
Date	25 April 2023
EU Post-Authorization Study (PAS) register number	EUPAS45356
Active substance	Rimegepant (formerly BHV-3000), Anatomical Therapeutic Chemical (ATC) code N02CD06
Medicinal product	Nurtec ODT™/Vydura®
Product reference	PF-07899801 (United States) EU/1/22/1645 (European Union)
Procedure number	EMEA/H/C/005725
Marketing Authorization Holder(s) (MAH)	Pfizer Inc. 66 Hudson Boulevard East New York, NY 10001 USA Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Bruxelles Belgium
Joint PASS	No
Research question and objectives	**Research Question**: Is there an increased risk of adverse fetal, maternal, and infant outcomes in women with migraines who were exposed to rimegepant during pregnancy?

	Primary Objective: To compare the occurrence of major congenital malformations (MCMs) in the fetuses/infants of women with migraine who were exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) with: 1) an internal cohort of women with migraine who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) and 2) an external cohort of pregnant women without migraine. **Secondary Objectives:** To compare the occurrence of the following secondary outcomes in women with migraine who were 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 who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) and 2) an external cohort of pregnant women without migraine. The secondary outcomes are as follows: • Minor congenital malformations • Pregnancy/fetal outcomes (recognized spontaneous abortion [SAB], elective termination, termination of pregnancy for fetal anomaly [TOPFA], stillbirth) • Maternal pregnancy complications (pre-eclampsia, eclampsia, gestational hypertension, gestational diabetes) • Infant outcomes (preterm birth and small for gestational age [SGA]) • Other adverse events (AEs), including infant events of interest (postnatal growth deficiency and infant developmental delay up to 1 year of age)
Country(-ies) of study	United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AEM	Adverse Event Monitoring
Ara-G	arabinosyl guanine
CDC	(US) 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
DCT	data collection tool
DES	diethylstilbestrol
EDC	electronic data capture
EDD	estimated date of delivery
EDP	exposure to a drug during pregnancy
EMA	European Medicines Agency
EU	European Union
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
HCP	healthcare provider
HIPAA	Health Insurance Portability and Accountability Act
IEC	Independent Ethics Committee
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century
IPW	inverse probability weighting
IRB	Institutional Review Board
IV	Intravenous
LMP	last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	major congenital malformation
MedDRA	Medical Dictionary for Regulatory Activities
MONITOR	Migraine Observational Nurtec Pregnancy Registry
NDA	New Drug Application
NIS	Non-interventional Study
NVSS	National Vital Statistics System
PAS	post-authorization study
PASS	post-authorization safety study
RCC	Registry Coordinating Center

Abbreviation	Definition
RMP	risk management plan
SAB	spontaneous abortion
SAC	Scientific Advisory Committee
SAE	serious adverse event
SAP	statistical analysis plan
SGA	small for gestational age
SOP	standard operating procedures
TERIS	Teratogen Information System
TOPFA	termination of pregnancy for fetal anomaly
US	United States
VRCC	Virtual Registry Coordinating Center
WHO	World Health Organization

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. 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)

Version 3.0, 25 April 2023

Kristin Veley, PharmD, MPH, PPD, part of Thermo Fisher Scientific

Rationale and background: Migraine prevalence is highest in women during child-bearing 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. In accordance with the European Union (EU) risk management plan (RMP), this study will satisfy the European Medicines Agency (EMA) requirement for a Category 3 post-authorization safety study (PASS) and additional pharmacovigilance activity to address the safety concern of rimegepant "use in pregnant women."

Research question and objectives: The primary research question is: "Is there an increased risk of adverse fetal, maternal, and infant outcomes in women with migraines exposed to rimegepant during pregnancy?" The purpose of the study is to prospectively evaluate fetal, maternal, and infant outcomes through 12 months of age in women with migraine who are 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 MCMs in the fetuses/infants of women with migraine who were 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 who are not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) and 2) an external cohort of pregnant women without migraine.
- The secondary objectives are to compare the occurrence of the secondary outcomes in women with migraine who were 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 during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) and 2) an external cohort of pregnant women without migraine. The secondary outcomes are as follows:
    - Minor congenital malformations
    - Pregnancy/fetal outcomes (recognized SAB, elective termination, TOPFA, stillbirth)

- Maternal pregnancy complications (pre-eclampsia, eclampsia, gestational hypertension, gestational diabetes)
- Infant outcomes (preterm birth and SGA)
- Other AEs, including infant events of interest (postnatal growth deficiency and infant developmental delay up to 1 year of age)

Study design: This study is an observational, prospective, pregnancy exposure registry of US pregnant women exposed to rimegepant and is in line with the current FDA guidance for designing and implementing pregnancy exposure registries.[3]

Population: The study population includes 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: 1) an internal cohort of women with migraine who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) 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
  - Currently or recently (within 12 months) pregnant women with migraine who were 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)
  - Currently or recently (within 12 months) pregnant women with migraine who were unexposed to rimegepant: a diagnosis of migraine and no exposure to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception)
- Reporter (eg, participant, maternal/infant healthcare provider [HCP]) contact information to allow for follow-up
- Permission to contact the patient's and her infant's HCPs
- Is personally signed and dated informed consent document, or upon waiver of written consent by the relevant institutional review board (IRB)/independent ethics committee (IEC), verbal consent indicating that the participant (or legally acceptable representative) has been informed of all pertinent aspects of the study

Exclusion:

- Women whose pregnancy outcome occurred >12 months prior to first contact with the registry

- Women who, at enrollment, have been exposed to other calcitonin gene-related peptide (CGRP) antagonists (eg, ubrogepant), CGRP monoclonal antibodies, or ditans (eg, lasmiditan) at any time during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception)

If needed, this exclusion criterion may be revised to include these participants.

Variables:

Exposure:

Exposure is defined as bodily update of any dose of rimegepant or other migraine product at any time during pregnancy (from conception to pregnancy outcomes) or just prior to pregnancy (up to 5 product half-lives prior to conception). Due to the short elimination half-life of rimegepant (11 hours), its pre-pregnancy exposure period 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.

Outcomes:

- Primary outcome: MCMs
- Secondary outcomes:
  - Minor congenital malformations
  - Pregnancy/fetal outcomes (recognized SAB, elective termination, TOPFA, stillbirth)
  - Maternal pregnancy complications (pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension)
  - Infant outcomes (preterm birth and SGA)
  - Other AEs, including infant events of interest (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 and their willingness to enroll in a registry is unknown. Therefore, we will conduct the first 3 years from study initiation as a feasibility assessment, aiming to enroll a minimum of 100 women with migraine who were exposed to rimegepant and 100 women with migraine who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception). 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. The EMA will also be sent the feasibility assessment. As needed, strategies will be considered to support increased

study enrollment. Contingent on enrollment success, the study will continue following the protocol timeline with the aim to enroll a minimum of 390 prospectively enrolled women with migraine who were exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception), as well as 390 women with migraine who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception). Each cohort of 390 is inclusive of its respective 100 feasibility study participants.

Comparisons will be made between 2 groups consisting of:

- Concurrently enrolled women with migraine who were 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 9.3.2). Women in this cohort may or may not be exposed to other migraine therapies during pregnancy.
- Pregnant women without migraine: 1) external published US background outcome rates among pregnant women without a diagnosis of migraine, and 2) the comparison population of the retrospective pregnancy outcomes study (New Drug Application [NDA] 212728, post-marketing requirement 3799-7, Pfizer study C4951006 [formerly BHV3000-403]) as an additional resource for non-migraine comparison group outcome rates of MCM, SAB, elective termination, stillbirth, pre-eclampsia/eclampsia, preterm birth, and SGA. Women in this cohort may or may not be exposed to medications during pregnancy.

Data analysis:

The main analysis population will include participants who are:

- Valid
- Prospectively enrolled
- Not exposed to other CGRP antagonists, CGRP monoclonal antibodies, and/or ditans after enrollment
- Not considered lost to follow-up

For some outcomes, the main analysis population will be further restricted based on certain relevant factors. Demographic characteristics, baseline characteristics, and prevalence rates of the outcomes of interest will be compared between the internal study cohorts: pregnant women with migraine who were exposed to rimegepant versus pregnant women with migraine who were unexposed to rimegepant.

Demographic and baseline characteristics will be summarized annually with descriptive statistics. Balance between cohorts will be assessed using standardized differences. These data will be presented before and after they are balanced with the inverse probability weighting (IPW) method. Reasons will be summarized for those excluded from the main analysis population, (ie, invalid, retrospectively enrolled, lost to follow-up).

Formal quantitative comparisons of the prevalence rates of the outcomes of interest will be conducted between the study cohorts. If the number of events permits, results for each outcome will be presented for 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 rimegepant (acute only, preventive only, or both), maternal age at conception (<18 years, 18–34 years, ≥35 years), and, for the analysis of MCM, preterm birth status (full term or preterm). Supplementary analyses will be conducted that include pregnant women who were excluded from the main analysis population due to: 1) the occurrence of a pregnancy outcome prior to enrollment (retrospectively enrolled participants) or 2) exposure to other CGRP antagonists, CGRP monoclonal antibodies, and/ditans after enrollment.

Sensitivity analyses will be conducted to evaluate: 1) exposure to known teratogens (eg, valproic acid and topiramate), 2) the impact of using a stricter definition of prospective enrollment, and 3) the impact of including congenital malformations that are chromosomal or genetic.

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

Milestones: The study became open for enrollment beginning on 23 September 2021. The estimated end of data collection is April 2034, and the final study report will be submitted by April 2035.

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
Original protocol	18 Aug 2021	Not applicable	Not applicable	Not applicable
Amendment 1	08 Nov 2022	Post-authorization safety study information Section 6 Milestones Section 7 Rationale and background Section 9.1 Study design Section 9.2 Setting Section 9.3 Variables Section 9.5 Study size Section 9.9 Limitations of the research methods	Protocol updated to align with European Medicines Agency's template for non-interventional post-authorization safety study protocols and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance checklist	To address comments received from Pharmacovigilance Risk Assessment Committee Assessment, Sep 2022
Amendment 2	25 Apr 2023	Whole document	Revised to Pfizer's protocol template	To reflect change of Sponsor
		Section 6 Milestones and 9.2 Setting	Updated enrollment start date to actual date	To reflect actual start date
		Section 9.2.2 Exclusion criteria	Added eligibility criteria to exclude "Women whose pregnancy outcome occurred >12 months prior to first contact with the registry."	To address potential recall bias
		Section 9.2.3 comparator groups Section 9.2.3.2 External comparator group Table 4. Calculation of outcome prevalence	Added elective termination and pre-eclampsia/eclampsia to other outcomes listed in text Added rows to table for MCM, pre-eclampsia / eclampsia, SAB, stillbirth, elective termination, preterm birth, SGA	To specify outcomes compared with Pfizer Study C4951006
		Section 9.2.4.1 Recruitment strategy	Added text to describe efforts to increase diversity	To reflect current awareness efforts
		Section 9.3.1 Registry participant management and disposition	Added section defining participant statuses	To provide additional detail regarding participant status definitions

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Section 9.3.4.9 Postnatal growth deficiency Section 9.3.4.10 Infant developmental delay	Added text to define outcomes	To ensure definitions for all outcomes are included
		Section 9.4.1, Table 1	Removed row for "migraine headache log" and added rows for "weekly log of migraine headaches and acute medications" and "monthly log for preventive migraine medications"	To reflect actual data collection forms
		Section 9.7.3.3. Calculation of outcome prevalence	Revised the denominator in the TOPFA comparison with the EUROCAT data to include stillbirths (in addition to livebirths)	To address a comment from the FDA, received Feb 2023
		Section 9.7.3.5 Subgroup analyses	Added subgroup analysis for MCM and preterm birth status	To further investigate the potential for increased risk of MCM among preterm infants
		Section 9.7.3.6 Supplementary analyses	Added bullet to reflect that participants with exposure to excluded medications (other CGRP antagonists, CGRP monoclonal antibodies, and/or ditans) after enrollment will be included in supplementary analyses	To align with rest of protocol, including Sections 9.3.1.3 and 9.7.1
		Annex 4. List of Known Teratogens	Updated information on teratogenic medications	To address comments from the FDA, received Feb 2023

6. MILESTONES

Milestone	Planned date	Actual date
Start of data collection	July 2021	23 September 2021
End of data collection	April 2034	
Registration in the EU PAS Register®	January 2022	26 January 2022
Interim study report 1	April 2022	Sent to FDA: April 2022 Sent to EMA: October 2022
Interim study report 2	April 2023	April 2023
Interim study report 3, including feasibility assessment	April 2024	
Interim study report 4	April 2025	
Interim study report 5	April 2026	
Interim study report 6	April 2027	
Interim study report 7	April 2028	
Interim study report 8	April 2029	
Interim study report 9	April 2030	
Interim study report 10	April 2031	
Interim study report 11	April 2032	
Interim study report 12	April 2033	
Final report of study results	April 2035	

EMA = European Medicines Agency; EU = European Union; FDA = Food and Drug Administration; PAS = post-authorization study

7. 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; one 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 women 18–29 years, 28.4% in women 30–39 years, and 25.8% in women 40–49 years.[1] Some studies noted that, in early pregnancy, approximately 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 more than 34,000 patients.[8]

7.1. Rimegepant and CGRP receptor antagonists

Nurtec ODT™ (rimegepant), a calcitonin gene-related peptide (CGRP) receptor antagonist developed by Biohaven Pharmaceuticals, Inc., 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. 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.[10,12] 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 September 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 them, more than 3,800 unique subjects have received the rimegepant clinical dose of 75 mg in the Phase 2 and Phase 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 (AEs).

7.2. 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.[14]

As of 31 May 2020, there were 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 spontaneous abortions (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.

Lastly, a study of breastfeeding women (lactation) with rimegepant (BHV3000-115) was initiated in Jan 2020.

7.3. Migraine and pregnancy outcomes

Migraine itself has been associated with an increased risk of some adverse pregnancy outcomes. A 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.[15] 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 small for gestational age (SGA) and MCMs. The prevalence of any MCM was 3.1% in women with and without migraine. Offspring who were 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.[15]

Other investigators have similarly reported associations between migraine and gestational hypertension, pre-eclampsia,[16] low birth weight,[8,16-18] and preterm birth.[8,16] In earlier studies, women with migraine were reported to be at an increased risk of developing hypertensive disorders such as pre-eclampsia in pregnancy compared to women without migraine,[19,20] which is associated with an increased risk of low birth weight, preterm birth, and SGA infants.[20-22] In the migraine population, more severe migraine,

defined by greater frequency and intensity, was shown to be associated with an increased prevalence of cardiovascular comorbidities and comorbid affective disorders such as anxiety and depression.[23,24] In the US general population, the estimated background risk of MCMs and miscarriage in clinically recognized pregnancies is 2%–4% and 15%–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.[14]

7.4. 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 acute and prophylactic treatments. The study found no increased risk associated with migraine treatment (acute, prophylactic, or both) for miscarriage, pregnancy-associated hypertension, adverse birth outcomes, including congenital malformations, or adverse neonatal or neurological outcomes in offspring,[15] including the outcomes of interest for this study.

Another challenge in evaluating maternal, fetal, and infant outcomes is the established association of some specific prophylactic and acute anti-migraine medications with congenital malformations and other study outcomes.[25] 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.[26-28] 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 to accurately contextualize event rates.

A medical need for the treatment of migraine during pregnancy may arise, with treatment decisions based on clinical judgment of the benefits and 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 who were exposed to rimegepant during pregnancy with 2 unexposed comparison populations is designed to satisfy the FDA post-marketing requirement for rimegepant (New Drug Application [NDA] 212728 Approval letter, 27 February 2020). The design and outcomes follow the FDA guidance on pregnancy safety studies[3] and experience from other pregnancy studies, including pregnancy exposure registries.

This non-interventional study is designated as a post-authorization safety study (PASS) and is a commitment to the US FDA, as well as a Category 3 commitment in the EU risk management plan (RMP) to address the safety concern “use in pregnant women.”

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research question

Is there an increased risk of adverse fetal, maternal, and infant outcomes in women with migraines who were exposed to rimegepant during pregnancy?

8.2. Objectives

The purpose of the study is to prospectively evaluate fetal, maternal, and infant outcomes through 12 months of age in women with migraine who were 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 who were exposed to rimegepant"), as well as in 2 comparison groups of women with and without migraine who were not exposed to rimegepant during pregnancy.

The primary objective is to compare the occurrence of MCMs in the fetuses/infants of women with migraine who were 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 who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) (hereinafter referred to in the main text as "pregnant women with migraine who were 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 in women with migraine who were 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 during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception) and 2) an external comparator cohort of pregnant women without migraine.

8.3. Outcomes

The primary and secondary outcomes are listed below.

8.3.1. Primary outcome

- MCMs

8.3.2. Secondary outcomes

- Minor congenital malformations
- Pregnancy/fetal outcomes (recognized SAB, elective termination, TOPFA, stillbirth)
- Maternal pregnancy complications (pre-eclampsia, eclampsia, gestational hypertension, gestational diabetes)
- Infant outcomes (preterm birth and SGA)

- Other AEs, including infant events of interest (postnatal growth deficiency and infant developmental delay up to 1 year of age)

9. RESEARCH METHODS

9.1. Study design

This study is a prospective, observational, pregnancy exposure registry of pregnant women with migraine who were exposed to rimegepant in the US conducted using primary data collection. The prevalence rates of the outcomes of interest in the exposed cohort will be compared with those of: 1) an internal cohort of pregnant women with migraine who were 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. All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and HCP specialty in the countries where this non-interventional study is being conducted.

9.2. Setting

This study is US-based. The study became open for enrollment on 23 September 2021. The data collection process for each participant will begin at enrollment, with data collection from 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 with the infant's HCP at 4 and 12 months after delivery. 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), has been submitted to the Center for Drug Evaluation and Research (CDER) beginning April 2022. The Interim Report summarizes the status and the cumulative data that are 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.

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 who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to

conception). 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.

9.2.1. Inclusion criteria

Participants must meet all of the following inclusion criteria to be eligible for inclusion in the study population (ie, "valid participant"):

1. Sufficient information to confirm eligibility:
    - Currently or recently (within 12 months) pregnant women with migraine who were 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)
    - Currently or recently (within 12 months) pregnant women with migraine who were unexposed to rimegepant: a diagnosis of migraine and no exposure to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception)
2. Reporter (eg, participant, maternal/infant HCP) contact information to allow for follow-up
3. Permission to contact the participant's and her infant's HCPs
4. Is personally signed and dated informed consent document, or, upon waiver of written consent by the relevant IRB/IECs, verbal consent, indicating that the participant (or a legally acceptable representative) has been informed of all pertinent aspects of the study

9.2.2. Exclusion criteria

Participants meeting any of the following criteria will not be included in the study:

1. Women whose pregnancy outcome occurred >12 months prior to first contact with the registry
2. Women who, at enrollment, have been exposed to other CGRP antagonists (e.g., ubrogepant), CGRP monoclonal antibodies, or ditans (eg, lasmiditan) at any time during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception)

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 (ie, multiple branded therapies)

At the end of the 3 years, and in consultation with the FDA, the success of the feasibility study (Section 9.5.1) 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.

Some participants included in the registry may be excluded from the statistical analysis (details in Section 9.7.1)

9.2.3. Comparator groups

The registry will include 2 comparator groups:

- **Pregnant women with migraine who are unexposed to rimegepant cohort:** migraine diagnosis (as defined in Section 9.3.2) and no exposure to rimegepant before or during the pregnancy period. Women in this cohort may or may not be exposed to other migraine therapies during pregnancy.
- **Pregnant women without migraine cohort:** 1) external published US background outcome rates among pregnant women without a diagnosis of migraine, 2) the comparison population of the retrospective pregnancy outcomes study (NDA 212728, post-marketing requirement 3799-7, Pfizer study C4951006 [formerly BHV3000-403]) as an additional resource for non-migraine comparison group outcome rates of MCM, SAB, elective termination, stillbirth, pre-eclampsia/eclampsia, preterm birth, and SGA. Women in this cohort may or may not be exposed to medications during pregnancy.

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

9.2.3.1. Internal comparator group

The internal comparator group will consist of women with migraine who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception), and who meet all of the study inclusion (Section 9.2.1) and exclusion (Section 9.2.2) criteria described above. While women with migraine who were untreated with any therapy could be included in this group, it is not expected to consist entirely of untreated women. Migraines are associated with some baseline pregnancy risks and comorbidities, and limiting to untreated comparisons may introduce bias by selecting a cohort of women with less-severe disease, or other fundamental population differences with potentially differential pregnancy outcomes.

9.2.3.2. External comparator group

For the external comparator group (pregnant women without migraine), the retrospective pregnancy outcomes study (NDA 212728, post-marketing requirement 3799-7, Pfizer study C4951006 [formerly BHV3000-403]) will serve as a resource for outcome rates of MCM, SAB, elective termination, stillbirth, pre-eclampsia/eclampsia, preterm birth, and SGA. Women in this cohort may or may not be exposed to medications. 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 comparators.

9.2.3.3. External published data

Published results from the Metropolitan Atlanta Congenital Defects Program (MACDP) for congenital malformations, European Surveillance of Congenital Anomalies (EUROCAT), as well as published data for other outcomes of interest (eg, the US 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. Thus, external sources are useful when assessing the generalizability of this study's findings and any other future study findings.

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

9.2.4. Participant recruitment and retention

9.2.4.1. 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 (eg, Migraine Buddy), and external data sources (eg, pharmacy claims or electronic medical records). The Sponsor's existing infrastructure for supporting stakeholders (eg, the Pfizer 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 will involve direct-to-HCP outreach, as well as online and print advertising directed to HCPs and patients. In addition, stakeholders may be identified and provided information regarding the registry via telephone through the Pfizer medical information call center, specialty pharmacies that dispense rimegepant, and the patient support program.

In an effort to increase the diversity of enrolled study participants, study materials (eg, study website, data collection forms, information sheet, and informed consents) will be available in US English and US Spanish. In addition, a translation vendor will be used to engage in real-time translation to/from US Spanish for existing and potential participants. Campaign materials will also depict diverse women and families.

9.2.4.1.1. 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.

9.2.4.1.2. 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

- Pfizer website
- PPD website

A web-based interface that is compatible with 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 (eg, 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 more than 90% of first-time expectant women in the US and more than 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.

9.2.4.1.3. 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 (eg, ultrasound clinics).

9.2.4.1.4. 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 Virtual Registry Coordinating Center [VRCC] to contact the potential participant and provide additional information about the registry)

9.2.4.2. Retention strategy

A retention strategy will be facilitated by engaging the participant and HCP; the goal will be 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 registry participants and HCPs. The specialized staff, many of whom are obstetric nurses, have experience collecting data for observational studies from patients and research-naïve 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 (ie, email, newsletters, and the registry website). The materials provided will emphasize the mission of the registry to promote participant engagement and direct participants to the website.

The registry will use streamlined data collection processes and simple, concise data collection forms that focus on the endpoints of interest to reduce the burden of reporting. The registry will provide multiple options for communication and data submission (eg, phone, fax, mail, email, website, web-based/mobile application), as well as 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 if 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 the HCPs involved in the pregnant women's care once the 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.

9.2.5. Considerations for generalizability of study population

The results from the prospective registry, although limited to US participants, will likely be generalizable to the general population in the US and the EU for several reasons:

1. Participants in clinical research in the US are predominantly white, and racially/ethnically diverse groups are underrepresented, despite efforts by the industry and regulators to increase diversity.[30,31] Pregnancy registries are not immune to this issue. As evidenced by several of the largest pregnancy registries conducted in the US and globally, the women who participate are predominantly white.[32-34] The demographic characteristics of women who participate in clinical research in the US, and specifically pregnancy registries, align with those of the general EU population.

2. The demographic characteristics of patients with migraine in the US are similar to those in the EU. In the US and the EU, patients with migraine are predominantly white and female, and the disease tends to more frequently affect individuals aged 18 to 44 years.[5,35] Gender-related differences are thought to stem from hormonal differences between males and females,[36] while race-related differences are thought to be attributable to differences in genetic vulnerability to migraine.[37]

The US-based prospective registry collects detailed demographic data, including age, race, ethnicity, education, employment status, and income, as well as anthropometrics such as height, weight, and body mass index. These will be compared with those of women of child-bearing potential with migraine in the US, their source population, and in the EU to identify any issues with representativeness, if needed.

Based on the information provided above, it is expected that the data collected via this US-based study will be generalizable to the EU population. The representativeness of the data will be evaluated in each interim report by comparing the demographic and clinical characteristics of registry participants with those from the published literature on pregnant women with migraine, including results from the pan-European ConcePTION project on migraine.[38,39]

9.3. Variables

9.3.1. Registry participant management and disposition

The following variables will be used to define inclusion in the main analysis population (defined in Section 9.7.1).

9.3.1.1. Valid versus invalid participants

A valid participant will be defined as a pregnant woman with sufficient data, submitted or confirmed by an HCP, for determining and meeting inclusion/exclusion into one of the study population cohorts. Participants who lack the minimum data required for determining inclusion or exclusion into one of the study cohorts or who lack confirmation from an HCP will be considered invalid. Participants who complete the ***Weekly Log for Migraine Headaches and Acute Medications*** and ***Monthly Log for Preventive Migraine Medications***, documenting their exposure to acute and preventive migraine therapies during pregnancy will not be required to have HCP confirmation of exposure. Invalid participants will be enumerated in each registry report but will not be included in statistical analyses.

9.3.1.2. Prospectively enrolled versus retrospectively enrolled participants

The registry will encourage prospective registration; however, retrospective enrollment in the registry will be permitted. A prospectively enrolled participant will be defined as a pregnant woman who enrolls or makes initial contact with the registry prior to the pregnancy outcome. A retrospectively enrolled participant will be defined as a pregnant woman who enrolls in the registry after the pregnancy outcome has occurred. The registry will retrospectively enroll participants up to 12 months after the occurrence of their pregnancy outcome.

Retrospectively enrolled participants can be biased toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population than prospectively enrolled participants. Therefore, retrospectively enrolled participants will be excluded from the main analysis population (Section 9.7.1) but will be analyzed separately in supplementary analyses (Section 9.7.3.6).

Diagnostic prenatal tests (eg, ultrasound to scan for structural defects at approximately 20 gestational weeks, chorionic villus sampling, and amniocentesis) can determine with high accuracy whether a fetus has a structural or chromosomal abnormality. Therefore, inclusion of women who have had diagnostic prenatal testing prior to enrollment in the main analysis population may introduce bias. To examine this potential bias, a sensitivity analysis that applies a stricter definition of prospective enrollment will be conducted (Section 9.7.3.7). 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.

9.3.1.3. Exposure to excluded products

Women will be considered exposed to excluded products (other CGRP antagonists, CGRP monoclonal antibodies, and/or ditans) during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (within a specified time based on the product's half-life). Participants will be considered exposed during pregnancy if a dose is taken prior to conception within a timeframe equivalent to 5 times the product's half-life.

Women who are exposed to excluded products during pregnancy and prior to study enrollment will not be permitted to enroll. Women who are enrolled but later exposed to excluded products (other CGRP antagonists, CGRP monoclonal antibodies, or ditans) will be excluded from the main analysis population (Section 9.7.1); however, these participants will be analyzed in supplementary analyses (Section 9.7.3.6).

9.3.1.4. Participants lost to follow-up

A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable after multiple attempts using various modes of communication; pregnant women without pregnancy outcome information will be considered lost to follow-up. Information from these participants (eg, baseline characteristics, abnormal prenatal test results, and reason for loss to follow-up, if available) will be summarized in each registry report, but these participants will be excluded from the main analysis population (Section 9.7.1). Live-born infants without follow-up data after birth will still have their pregnancy-related information included in the main analysis population.

9.3.1.5. Multiple-gestation pregnancies

Multiple-gestation pregnancies will be enrolled in the registry. Each fetus/infant will be assigned a unique identifier and included in the main analysis population (Section 9.7.1); however, for the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple-gestation pregnancies will be excluded from the main analysis population due to the higher risk of these outcomes in twins and higher-order multiples.

9.3.2. 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 will be consistent with the International Classification of Headache Disorders, Third Edition.[4] Disease information, including date of diagnosis and disease severity, will be collected from HCPs and/or participants.

9.3.3. Exposure of interest

Exposure to rimegepant is a condition for inclusion into the cohort of pregnant women with migraine who were exposed to rimegepant. In addition, pregnant women who were 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 who were unexposed to rimegepant. Finally, participants who were exposed to other CGRP antagonists (eg, ubrogepant), CGRP monoclonal antibodies, or ditans (eg, lasmiditan) will not be eligible for enrollment into either cohort. ANNEX 3 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 will be 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, at the end of the second trimester, and at the occurrence of the 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 9.4.1 for more information.

Exposure will be further categorized by trimester of exposure; Section 9.4.3 provides information on the methods used to determine gestational age and trimester of exposure.

9.3.4. Outcomes

9.3.4.1. Congenital malformations

The study will define and code congenital malformations using the criteria specified by the CDC MACDP and EUROCAT.[40,41] A malformation may be described and classified by severity (eg, major malformation), by origin (eg, genetic, environmental exposure), and by organ system (eg, urogenital system or malformations known as congenital heart defects [CHD]). An MCM will be 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.[40] This definition is consistent with, but not restricted to, the CDC MACDP and EUROCAT definitions.

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 (eg, patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (eg, 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.[42] Given that the registry will also use the CDC's MACDP and EUROCAT as external comparators, the registry will include cases of MCMs not associated with medication exposure in the 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 (eg, CHDs).[43] Lastly, the MACDP only includes minor malformations if they occur 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 has different objectives and reporting needs than this project, 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, including: 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.

9.3.4.2. Pregnancy outcome

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

- 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. Participants who have an elective termination will be further categorized based on presence of fetal anomalies:
- TOPFA: voluntary interruption of pregnancy after prenatal diagnosis[44] of fetal anomaly
- Stillbirth: a fetal death occurring at ≥20 gestational weeks, or if gestational age is unknown, a fetus weighing ≥350 g
- Live birth: an infant born alive (any Apgar score >0)

9.3.4.3. Pre-eclampsia

Pre-eclampsia will be defined as high blood pressure and signs of liver or kidney damage (eg, proteinuria) occurring at >20 gestational weeks.[45,46]

9.3.4.4. Eclampsia

Eclampsia will be defined as seizures or coma in a pregnant woman with pre-eclampsia.[45]

9.3.4.5. Gestational hypertension

Gestational hypertension will be defined as high blood pressure occurring at >20 gestational weeks without signs of liver or kidney damage (eg, proteinuria).[46]

9.3.4.6. Gestational diabetes

Gestational diabetes will be defined as any degree of glucose intolerance with onset or first recognition during pregnancy.[47]

9.3.4.7. Preterm birth

Preterm birth will be defined as an infant born at <37 weeks gestational age. 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).

9.3.4.8. Small for gestational age (SGA)

SGA will be defined as birth weight <10th 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 infants born between $24^{0/7}$ and $42^{6/7}$ gestational weeks.[48,49] 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.

9.3.4.9. Postnatal growth deficiency

Postnatal growth deficiency will be defined as weight, length, or head circumference in < 10th percentile for sex and chronological age using standard growth charts.[50]

9.3.4.10. Infant developmental delay

Infant development delay will be defined as failure to achieve developmental milestones for chronological age, as defined by the CDC.[51]

9.3.5. Other variables

The following additional variables will be collected (or derived from collected data):

- 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 (eg, congenital uterine abnormalities)

- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia, preterm labor, placental abruption, and incompetent cervix
- Number of previous pregnancies
- Previous pregnancy outcomes (SAB, stillbirth, elective termination, TOPFA, 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 (ie, to establish baseline severity) and duration (ie, 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

9.4. Data sources

9.4.1. 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 timepoints: at enrollment, at the end of the 2nd 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 timepoints: 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 forms 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 9.4.1.1, 9.4.1.2 and 9.4.1.3 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 • Maternal demographic characteristics • Maternal pre-pregnancy anthropometrics • Disease information
Weekly Log for Migraine Headaches and Acute Medications	Participant	At enrollment, then in real time or in near real time, and submitted weekly during pregnancy	• Disease information • Maternal exposures to acute migraine medications during pregnancy
Monthly Log for Preventive Migraine Medications	Participant	At enrollment, then in real time or in near real time, and submitted monthly during pregnancy	• Maternal exposures to preventive migraine medications during pregnancy
Registration Form for HCPs	Obstetric HCP and prescribing HCP, if needed	Enrollment	• Registration information, including eligibility criteria • Maternal obstetrical history • Family history of congenital malformations • Disease information • Baseline pregnancy information
Pregnancy Information Form	Obstetric HCP and prescribing HCP, if needed	Enrollment, end of 2nd trimester[a], and EDD/pregnancy outcome[a]	• Ongoing pregnancy information • 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

9.4.1.1. Information collected at enrollment

After applicable informed consent is obtained from the eligible women, the following information will be collected on the ***Registration Form for Participants***, ***Registration Form for Healthcare Providers***,

Weekly Log for Migraine Headaches and Acute Medications, ***Monthly Log for Preventive Migraine Medications,*** 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

- On a weekly basis, exposure to rimegepant or other acute migraine therapies (prescription and non-prescription), including name of product, dates of exposure, and total dose taken on each day of the week, if available
- On a monthly basis, exposure to rimegepant or other preventive migraine therapies (prescription and non-prescription), including name of product, dates of exposure, dose, route, and frequency

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 will only be asked 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, and 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.

9.4.1.2. Information collected at pregnancy follow-up

Near 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, follow-up at the end of the second trimester 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 will also be contacted to authorize the 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

- On a weekly basis, exposure to rimegepant or other acute migraine therapies (prescription and non-prescription), including name of product, dates of exposure, and total dose taken on each day of the week, if available
- On a monthly basis, exposure to rimegepant or other preventive migraine therapies (prescription and non-prescription), including name of product, dates of exposure, dose, route, and frequency

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 will only be asked 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, and 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

- On a weekly basis, exposure to rimegepant or other acute migraine therapies (prescription and non-prescription), including name of product, dates of exposure, and total dose taken on each day of the week, if available
- On a monthly basis, exposure to rimegepant or other preventive migraine therapies (prescription and non-prescription), including name of product, dates of exposure, dose, route, and frequency

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 will only be asked 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 (eg, 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 (SAB, elective termination, TOPFA, live birth, stillbirth)

- Date of pregnancy outcome
- 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
- For live birth, prolonged hospitalization after birth

9.4.1.3. Information collected at pediatric follow-up

Timing of pediatric follow-up

If a live birth occurs, the mother will be asked to authorize the 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.[52]

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 of an event of interest

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

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 9.4.4)

9.4.2. Follow-up process

Attempts to obtain the follow-up information

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. Three subsequent attempts will be made every 2 weeks via various modes of communication (eg, phone, fax, email, mail), as necessary. If no response is received from the HCP, additional attempts may occur at the next planned data collection time point (eg, 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 contact attempts will be made. The reason the participant was lost to follow-up (eg, no response from HCP, no response from participant, or participant withdrawal of consent) will be documented.

Follow-up process for clarification of information

If there are outstanding questions, discrepancies between forms, or missing data for critical data points, 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.

9.4.3. Operational exposure definition

When a pregnant woman self-enrolls in the study, she will be asked about her treatment history with rimegepant. The pregnant woman will then be asked to provide a medical release that allows the VRCC

to confirm with the appropriate source any dates of specified rimegepant treatment pre-pregnancy or during pregnancy and ascertain the indication for prescription (ie, 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 was never estimated, the first day of the LMP may be used to estimate gestational age. The 2nd trimester will be considered to begin at Week 14 after LMP, and the 3rd trimester at Week 28. If there is a discrepancy between the gestational age calculated from LMP and the reported gestational age, the HCP will be asked to verify the data.

9.4.4. Operational malformation definition and identification process

All variables for the pregnancy outcomes and maternal/infant events of interest will be provided by the treating or obstetric HCP and the infant's pediatric HCP. If no data on the pregnancy outcome can be obtained from the HCP, the pregnant woman will be asked to provide this information. The HCP will also be asked to describe any congenital malformations observed in the infant or fetus at birth.

A panel of 2 independent experts in clinical genetics, teratology, or neonatology will serve as birth defect evaluators, will review all reported congenital malformations, and will classify them using the CDC's MACDP and EUROCAT systems, as specified in Section 9.3.4.1. If there is a discrepancy, a 3rd independent evaluator will review and code the case, serving as a 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 the 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 and EUROCAT),[40] and a classification system, developed to facilitate the ability to generate potential signals.[53] 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 using the information available.

Once the exposure status blinding is broken following the review, the SAC (see section 9.8.2) review will include 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 using the information available.

The assessments of temporality with the registry drug exposure will be classified as 1 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

9.4.5. Other operational variable(s) definition

As is indicated in Section 9.4.1, women who self-enroll will provide their maternal characteristics at study enrollment. After the woman provides consent and authorizes the 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 asked to provide pregnancy outcome data (SAB, elective termination, TOPFA, stillbirth, live birth), delivery data, and infant outcome data (including but not limited to gestational age, birth weight, length, head circumference, and sex). If data on the pregnancy outcome cannot be obtained from the HCP, the woman will be asked to provide this information. 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.

9.5. Study size

9.5.1. 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. Therefore, we will conduct the first 3 years from study initiation as a

feasibility assessment, aiming to enroll a minimum of 100 women with migraine who were exposed to rimegepant during pregnancy or just prior to pregnancy (up to 3 days prior to conception) and 100 women with migraine who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception). 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. The EMA will also be sent the feasibility assessment. As needed, strategies will be considered to support increased study enrollment, including expanding the registry to countries outside the US and exercising the option to revise the study exclusion criteria to include women exposed to other CGRP antagonists (eg, ubrogepant), CGRP monoclonal antibodies, or ditans (eg, 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 outlined in the section that follows (the sample size below is inclusive of the feasibility sample).

9.5.2. Full study

The full study will aim to prospectively enroll a minimum of 390 women with migraine who were 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 who were not exposed to rimegepant during pregnancy or just prior to pregnancy (up to 5 product half-lives prior to conception). 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 1 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,[54] at α=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.[55] A midpoint threshold of a 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, post-marketing requirement 3799-7, Pfizer study C4951006 [formerly 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.[56,57] Assuming that 90% of prospectively enrolled pregnancies result in live births and 10% are lost to follow-up,[58] at α=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[b]
MCM	390	3%[54,55,59]	2.5	80.6%
MCM	316[a]	3%[54,55,59]	2.7	80%

MCM = major congenital malformation; reference rate = prevalence rate of outcome in general population for pregnant women of any age

[a] Assumes that 90% of prospectively enrolled pregnancies result in live births and 10% are lost to follow-up, resulting in 316 evaluable participants

[b] Power calculations based on normal approximation, 2-tailed, α=0.05[60]

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, stillbirth, and TOPFA (for which the study will have <20% power to detect a 2.5-fold increase).

Table 3. Power Calculations

Outcome	Reference rate	Power estimate[a]
MCM[54,55,59]	3%	80.6%
Gestational diabetes[29]	6.9%	>99.0%
Gestational hypertension[61]	6.5%	>99.0%
Pre-eclampsia[62]	3.40%	85.5%
Eclampsia[61]	0.3%	2.7%[b]
SAB[63]	13.4%	>99.0%
Stillbirth[64]	0.596%	12.6%[b]
Elective termination[65]	18.6%	>99.0%
TOPFA[66]	0.4%	5.8%[b]
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; TOPFA = termination of pregnancy for fetal anomaly.

*By Definition

[a] Power calculations were conducted using nQuery and were based on normal approximation, 2-tailed, alpha 0.05.

[b] Fisher's Exact test was used for power calculation.

9.6. Data management

9.6.1. Case report forms (CRFs)/Data collection tools (DCTs)/Electronic data record

As used in this protocol, the term DCT should be understood to refer to a paper data collection form or an electronic data record or both, depending on the data collection method used in this study.

A completed DCT is required for each included participant. The completed, original DCTs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer. PPD shall ensure that the DCTs are securely stored in encrypted electronic form and will be password protected to prevent access by unauthorized third parties.

PPD has ultimate responsibility for the collection and reporting of all data entered on the DCTs, as required, and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The DCT serves as the source document. Any corrections to entries made in the DCTs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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. The variables described in Section 9.4.1 will be solicited and entered in the EDC directly by participants and/or their HCPs or indirectly by VRCC personnel. The data provided by participants and/or their HCPs over the phone or on paper data collection forms, which can be submitted to the VRCC via mail, email or fax, will be reviewed for correctness and completeness and entered into the database by VRCC personnel.

Free-text entries of medical conditions, including AEs and medicinal exposures will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and World Health Organization (WHO) Drug, respectively. All free-text data will be reported in listings.

9.6.2. Software and hardware

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

9.6.3. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, PPD agrees to keep all study-related records. The records should be retained by PPD according to local regulations or as specified in the vendor contract, whichever is longer. PPD must ensure that the records continue to be stored securely for so long as they are retained.

If PPD becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless PPD and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Records must be retained for longer than 15 years if required by applicable local regulations.

PPD must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.7. Data analysis

Detailed methodology for the summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed, and maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary outcome definitions or their analyses would be reflected in a protocol amendment.

Descriptive analyses for the primary and secondary study objectives will be performed annually for all data; 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 characteristics, baseline characteristics, and prevalence rates of the outcomes of interest will be conducted between the study cohorts: pregnant women with migraine who were exposed to rimegepant versus pregnant women with migraine who were unexposed to rimegepant.

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.

9.7.1. Main analysis population

The main analysis population will include participants who are:

- Valid (Section 9.3.1.1)
- Prospectively enrolled (Section 9.3.1.2)
- Not exposed to other CGRP antagonists, CGRP monoclonal antibodies, and/or ditans after enrollment (Section 9.3.1.3)
- Not considered lost to follow-up (Section 9.3.1.4)

For some outcomes, the main analysis population will be further restricted based on certain relevant factors.

9.7.2. 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 inverse probability weighting (IPW) method (Section 9.7.3.4). Reasons will be provided for those excluded from the main analysis population (ie, invalid, retrospectively enrolled, lost to follow-up).

9.7.3. Analysis of the outcome measures

9.7.3.1. 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 9.7.3.3.

For each outcome, if the number of events permits, results will be presented for 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, SAB, elective termination, TOPFA, stillbirth, pre-eclampsia, eclampsia, gestational hypertension, gestational diabetes, 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 9.7.3.4). 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.

9.7.3.2. 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 main analysis population with those of selected external comparators (eg, MACDP, EUROCAT, NVSS), if available. Prevalence rates of the outcomes of interest will be calculated as described in Section 9.7.3.3. 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.

9.7.3.3. 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.[67]

For most outcomes, the main 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 timepoint of interest, as appropriate; however, for some outcomes, the main 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 (ie, 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 main analysis population (denominator).
- For infant developmental delay, infants born preterm will be excluded from the main 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 timepoints. For example, postnatal growth deficiency and infant developmental delay will be assessed at 2, 4, 6, and 12 months of

infant age. At each timepoint, prevalence will be calculated among infants with data available for the particular outcome at that timepoint.

For comparison with external comparators, the prevalence rates of the outcomes of interest among the rimegepant-exposed participants of the main analysis population will be calculated according to the conventions used by the selected external comparators. For example, for the 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 the 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 main 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 1st 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 1st trimester (if applicable)	Live births among women with pregnancy outcome data and, if applicable, exposure during 1st trimester
Secondary analysis: among all pregnancy outcomes with 1st 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 1st trimester	Live births and fetal losses among women with pregnancy outcome data and, if applicable, exposure during 1st 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 applicable, exposure at any time during pregnancy	Live births and fetal losses among women with pregnancy outcome data and, if applicable, exposure at any time during pregnancy

Outcome	Numerator	Denominator
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 1st trimester	Live births among women with pregnancy outcome data and exposure during the 1st trimester
Comparison with external comparator (Pfizer Study C4951006 [formerly BHVN Outcomes Study])	Live births with confirmed MCMs (excluding MCMs not associated with medication exposure) among women with pregnancy outcome data and exposure at any time during pregnancy	Live births among women with pregnancy outcome data and exposure at any time during pregnancy
Comparison with EUROCAT	Live births and stillbirths and TOPFA with confirmed MCMs (including MCMs not associated with medication exposure) among women with pregnancy outcome data and exposure during the 1st trimester	Live births and stillbirths among women with pregnancy outcome data and exposure during the 1st 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[61]	Gestational hypertension among live births	Live births among women with pregnancy outcome data
Pre-eclampsia		
Primary analysis between internal cohorts	Pre-eclampsia 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[61]	Eclampsia among live births	Live births among women with pregnancy outcome data
Pre-eclampsia/eclampsia		
Primary analysis between internal	Pre-eclampsia or eclampsia among	Women with pregnancy outcome

Outcome	Numerator	Denominator
cohorts	women with pregnancy outcome data	data
Comparison with external comparator (Pfizer Study C4951006)	Pre-eclampsia or eclampsia among women with pregnancy outcome data	Women with pregnancy outcome data
SAB		
Primary analysis between internal cohorts	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
Comparison with external comparator (Pfizer Study C4951006)	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
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
Comparison with external comparator (Pfizer Study C4951006)	Stillbirths among women with pregnancy outcome data	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
Comparison with external comparator (Pfizer Study C4951006)	Elective terminations among women with pregnancy outcome data	Women with pregnancy outcome data
TOPFA		
Primary analysis between internal cohorts	TOPFA among women with pregnancy outcome data	Women with pregnancy outcome data
Comparison with external comparator (EUROCAT)[44]	TOPFA among women with pregnancy outcome data	Live births and stillbirths among women with pregnancy outcome data
Preterm birth		
Primary analysis between internal cohorts	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
Comparison with external comparator (Pfizer Study C4951006)	Preterm live births among women with pregnancy outcome data who are	Live births among women with pregnancy outcome data who are

Outcome	Numerator	Denominator
	enrolled (and exposed, if applicable) prior to 37 gestational weeks	enrolled (and exposed, if applicable) prior to 37 gestational weeks
SGA		
Primary analysis between internal cohorts	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
Comparison with external comparator (Pfizer Study C4951006)	Live births who are SGA based on weight among women with pregnancy outcome data	Live births among women with pregnancy outcome data
Postnatal growth deficiency		
Primary analysis between internal cohorts (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		
Primary analysis between internal cohorts (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 = US Centers for Disease Control and Prevention; EUROCAT = European Surveillance of Congenital Anomalies; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; NVSS = National Vital Statistics System; SAB = spontaneous abortion; SGA = small for gestational age; TOPFA = termination of pregnancy for fetal anomaly

9.7.3.4. 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.[68-70] 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.

After the incorporation of weights, the regression model for each outcome may be further adjusted by incorporating covariates that remain imbalanced after weighting or are removed from the IPW model for causing convergence or imbalance issues.

9.7.3.4.1. Potential covariates and confounders

In accordance with guidance from the FDA and the Agency for Healthcare Research and Quality,[3,71] all of the covariates and confounders described in Section 9.3.5 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.

9.7.3.5. 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)
- For the analysis of MCM, preterm birth status (full term or preterm)

9.7.3.6. Supplementary analyses

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

- Occurrence of the pregnancy outcome prior to enrollment (retrospectively enrolled participants)
- Exposure to other CGRP antagonists, CGRP monoclonal antibodies, and/or ditans after enrollment

9.7.3.7. 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 (eg, valproic acid and topiramate) from the main 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 (ANNEX 4) and will be continually updated based on the data available in the Teratogen Information System (TERIS) database of teratogenic agents and recent publications.[72-74]

- 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.

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

9.7.4. Missing data

For critical data points, missing values are expected to be minimal, thereby negating the need for imputation. As described in Section 9.4.2, 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.

9.8. Quality control

9.8.1. Validation

Ensuring that the data obtained are of high quality will be an ongoing, multi-step process involving 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 VRCC 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.

9.8.2. Scientific Advisory Committee

An 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 in 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 (that have been classified by independent birth defect evaluators) other study outcomes; to carry out any actions required, including review and interpretation of interim data analyses and reports; and to 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.

9.9. Limitations of the research methods

As participation in the study will be voluntary, the included participants may not be representative of the overall population of pregnant women in the US and EU. 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. Therefore, 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 (ie, 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 be present.

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. Due to 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, the proportion of pregnancies lost to follow-up in each cohort will be compared to examine differential loss to follow-up, and the characteristics of those lost to follow-up will be compared to those not lost to follow-up within each cohort to address this potential source of bias.

The percentage of fetal losses (SABs, elective terminations, stillbirths, etc.) with 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 pre-eclampsia, and comorbidities, including cardiovascular comorbidities and affective disorders such as anxiety and depression.[23,24] It will be important to compare the pregnant women with migraine who were exposed to rimegepant and pregnant women with migraine who were unexposed to rimegepant 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, post-marketing requirement 3799-7, Pfizer

study C4951006 (formerly BHV3000-403); representing the pregnant women without migraine cohort), and data from the general population will be evaluated to contextualize observed occurrences of select outcomes in the registry.

An important potential limitation of this pregnancy registry is the possibility of lower-than-expected enrollment. This is possible 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 who were unexposed to rimegepant may have been treated with other prescribed or over-the-counter migraine therapies (eg, 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. A sensitivity analysis will be conducted that excludes participants exposed to known teratogens. Additionally, there may be differences in migraine severity between the cohort of pregnant women with migraine who were exposed to rimegepant and the comparison cohort of pregnant women with migraine who were unexposed to rimegepant. The impact of migraine itself will be considered by describing and, where possible, evaluating the relative occurrence of the study outcomes in the pregnant women with migraine who were exposed to rimegepant cohort and the pregnant women with migraine who were 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, post-marketing requirement 3799-7, Pfizer study C4951006 [formerly 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 to draw meaningful conclusions using the registry data.

Another major limitation of this study is the use of a composite, heterogeneous outcome, any MCM, as the primary outcome. The study is not powered to detect increases in the risk of individual defects, and it is necessary to aggregate all MCMs as a single outcome. However, because teratogens typically do not affect all organs equally, risk estimates will be biased toward the null. This will be considered when interpreting the results.

9.10. Other aspects

Not applicable.

10. 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 (ie, PPD), the central registry site (principal investigator, medical monitor, and VRCC), 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 the pregnant women and their infants.

Each employee in the VRCC 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 VRCC staff must train and test on these privacy SOPs annually.

As a post-marketing 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 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.[75]

10.1. Patient information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. PPD will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, PPD shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. PPD will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to their actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the vendor contract, research agreement, and applicable privacy laws.

10.2. Patient 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.

10.2.1. 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.

10.2.2. Electronic informed consent process

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

Once the woman has registered, the application will automatically start the consent process. The application will present the contents of the consent form 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 VRCC, 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 process, the woman will complete the medical release form(s) and answer some basic medical information questions.

10.2.3. 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:

1. An adequate plan is provided to protect the identifiers from improper use and disclosure.
2. An adequate plan is provided to remove the identifiers at the earliest opportunity.
3. 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.

10.3. Patient withdrawal

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of PPD for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document outcomes, if applicable. PPD would inquire about the reason for withdrawal and follow-up with the participant regarding any unresolved AEs.

If the participant withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The Sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional Review Board/Independent Ethics Committee

It is the responsibility of PPD to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (e.g., statement regarding agreement to participate), and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/Independent Ethics Committee (IEC). All correspondence with the IRB/IEC should be retained by PPD. Copies of IRB/IEC approvals should be forwarded to Pfizer.

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor, and follow generally accepted research practices described in the Guidelines for Good Pharmacoepidemiology Practices.[76]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

The table below summarizes the requirements for recording safety events on the data collection form and for reporting safety events on the Non-interventional Study (NIS) Adverse Event Monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: 1) serious AEs (SAEs); 2) non-serious AEs (as applicable); and 3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in the section "Definitions of safety events."

Note that SAEs requiring adjudication by the External Adjudication Committee (ie, any malformation) are not reportable to Pfizer Safety.

Table 5. Safety Event Reporting Requirements

Safety Event	Recorded on the data collection forms	Reported on the NIS AEM Report Form to Pfizer Safety within 1 Business Day / 3 Calendar Days[a] of Awareness
SAE	All	All[b]
Non-serious AE	All	None
Scenarios involving exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy	All (regardless of whether associated with an AE)	All (regardless of whether associated with an AE/ SAE) Note: Any associated AE is reported together with the exposure scenario.
Scenarios involving EDP	All AE or SAEs associated with EDP and EDP associated with	All SAEs[b] associated with EDP and EDP associated with off-label use (e.g., use in pediatric patients)

Safety Event	Recorded on the data collection forms	Reported on the NIS AEM Report Form to Pfizer Safety within 1 Business Day / 3 Calendar Days[a] of Awareness
	off-label use (eg, use in pediatric patients) Notification of EDP alone (ie, not associated with an AE or SAE or off-label use) is not required when the study population is pregnant women.	Notification of EDP alone (ie, not associated with an SAE or off-label use) is not required when the study population is pregnant women.
Scenarios involving occupational/environmental exposure	Not applicable	All (regardless of whether associated with an AE/SAE)

AE = adverse event; AEM = adverse event monitoring; EDP = exposure to a drug during pregnancy; NIS = non-interventional study; SAE = serious adverse event

[a] Whichever is shorter. If a national or state holiday falls directly before or after a weekend (resulting in ≥3 consecutive calendar days of closure), the reporting will be done the next business day.

[b] Except for SAEs judged by the External Adjudication Committee [i.e., any malformations]). Of note, adjudicated SAEs of which an HCP has indicated that SAE to have a causal relationship with rimegepant or other medications used to treat migraine are not included within this exception and must be reported to Pfizer Safety.

For each safety event, the PPD VRCC must pursue and obtain adequate information to determine the outcome and to assess whether it meets the criteria for classification as an SAE (refer to section "Serious Adverse Events" below).

Safety events must be reported per the process noted in Table 5 **regardless of whether the event is determined by the HCP to be related to rimegepant**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. The timeframe noted in Table 5 also applies to additional, new (follow-up) information on previously forwarded safety event reports. In the rare situation that the PPD VRCC does not become immediately aware of the occurrence of a reportable safety event, the PPD VRCC must report the event within 1 business day/3 calendar days**Error! Bookmark not defined.** after learning of i t and document the time of first awareness of the events on the NIS AEM Report Form.

For all safety events that are mentioned in the far-right column of Table 5, the PPD VRCC is obligated to pursue and to provide any additional information to Pfizer with the same reporting timeline. In addition, the PPD VRCC may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the data collection forms. In general, this will include a description of the safety event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

This protocol will use an external Endpoint Adjudication Committee wherein, to maintain scientific integrity, and adjudication of some clinical endpoints (ie, any malformations) defined in the study objectives will be performed. The Endpoint Committee is responsible for ongoing analysis of any malformations and of their adjudication as endpoints. Any malformation that is not adjudicated as an endpoint by the Endpoint Committee is reportable and is forwarded to Pfizer Safety. In addition, when the HCP has judged a malformation to have a causal relationship with rimegepant or other medications used to treat migraine, the PPD VRCC must still report it to Pfizer Safety, even if that event is a component of the adjudicated endpoint.

11.1. Reporting period

For each patient, the reporting period will begin at the time of the patient's first dose of rimegepant or other medications used to treat migraine, or the time of the patient's informed consent if s/he is being treated with rimegepant or other medications used to treat migraine at study start, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of the drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any safety events (as per Table 5) occurring during this period. If a patient is administered rimegepant or other medications used to treat migraine on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation, failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient.

If the PPD VRCC becomes aware of an SAE occurring at any time after completion of the study and the SAE has been reported as related to rimegepant or other medications used to treat migraine by the HCP, the SAE also must be reported to Pfizer Safety.

11.2. Causality assessment

An HCP's causality assessment is the determination of whether there exists a reasonable possibility that rimegepant or other medications used to treat migraine caused or contributed to the safety event. For all safety events, sufficient information should be obtained by the investigator to determine the causality.

In this study, unlike a trial design with sites and investigators, reporting HCPs will not have received formal training on providing causality assessments for the study drug. Further, given limited known information about the safety of rimegepant in pregnancy, it is expected that the HCPs will rarely provide a causality assessment for the reportable safety events, or they will report it as "unknown" as s/he cannot determine it. *In this event, the applicable, reportable safety event must still be reported to Pfizer Safety per the process outlined in* Table 5.

If the HCP cannot determine the etiology of the event but s/he determines that rimegepant or other medications used to treat migraine did not cause the event, this should be clearly documented on the data collection forms and the NIS AEM Report Form.

For all safety events with a causal relationship to rimegepant or other medications used to treat migraine, follow-up by the PPD VRCC is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the PPD VRCC, and Pfizer concurs with that assessment.

11.3. Definitions of safety events

11.3.1. Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an AE)
- Clinically significant signs and symptoms
- Changes in physical examination findings
- Hypersensitivity
- Progression/worsening of underlying disease
- Lack of efficacy
- Drug abuse
- Drug dependency

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose
- Drug withdrawal
- Drug misuse
- Off-label use
- Drug interactions
- Extravasation
- Exposure during pregnancy
- Exposure during breast feeding
- Medication error

- Occupational exposure

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE are as follows:

- Test result is associated with accompanying symptoms
- Test result requires additional diagnostic testing or medical/surgical intervention
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy
- Test result is considered to be an AE by the HCP or Sponsor

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE.

11.3.2. Serious adverse events

An SAE is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute SAEs)
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions)
- Results in congenital anomaly/birth defect

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory

findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported:

- Social admission (eg, patient has no place to sleep)
- Administrative admission (eg, for yearly exam)
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality)

11.3.3. Scenarios necessitating reporting to Pfizer Safety within 1 business day/3 calendar days

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An EDP occurs if:

- A female becomes, or is found to be, pregnant while receiving or having been exposed to the drugs under study, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to the drugs under study *(maternal exposure)*
- A female nonparticipant is found to be pregnant while being exposed or having been exposed to study intervention because of occupational or environmental exposure (eg, a female family member or HCP reports that she is pregnant and has been exposed to the product)

This information must be submitted to Pfizer Safety following the same reporting timeline and using the NIS AEM Report Form and the EDP Supplemental Form. Prospective and retrospective EDP reports are reportable to Pfizer Safety following the requirement described in Table 5.

All reports submitted should include the anticipated date of delivery, as applicable, and should be managed as follows:

- Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown.
- A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report.
- In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth.
- In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE as listed below, the procedures for reporting to Pfizer Safety (per Table 5) should be followed:

- Fetal outcomes (recognized SABs [including miscarriage and missed abortion], elective terminations, TOPFA, stillbirths, major and minor congenital malformations)
- Maternal pregnancy complications (including but not limited to pre-eclampsia, eclampsia, gestational hypertension, gestational diabetes)
- Neonatal deaths that occur within 1 month of birth without regard to causality.
    - In addition, infant deaths after 1 month should be reported when the HCP assesses the infant death as related or possibly related to exposure to investigational product.
- Infant outcomes (including but not limited to preterm birth and SGA)
- Other AEs, including infant events of interest (including but not limited to postnatal growth deficiency and infant developmental delay up to 1 year of age)

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

<u>Exposure during breastfeeding</u>

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing, or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the HCP, patient, or consumer. Such events may be related to professional practice, healthcare products, procedures, and systems, including prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the HCP or the patient/consumer)
- Confusion with regard to invented name (eg, trade name, brand name)

The PPD VRCC must submit the following medication errors to Pfizer Safety, irrespective of the presence of an associated AE/SAE:

1. Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE

2. Medication errors that do not involve a patient directly (eg, potential medication errors or near misses)
    - When a medication error does not involve patient exposure to the product, the following minimum criteria constitute a medication error report:
        - An identifiable reporter
        - A suspect product
        - The event medication error

Overdose, misuse, extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer Safety by the PPD VRCC, irrespective of the presence of an associated AE/SAE.

Lack of efficacy

Reports of lack of efficacy of a Pfizer product are reported to Pfizer Safety by the PPD VRCC, irrespective of the presence of an associated AE/ SAE or the indication for use of the Pfizer product.

Occupational/Environmental exposure

Reports of occupational exposure are reported to Pfizer Safety by the PPD VRCC, irrespective of the presence of an associated AE/SAE.

Since the information about the occupational exposure does not pertain to a participant enrolled in the study, the information is not recorded on a data collection form; however, a copy of the completed NIS SAE Report Form must be maintained in the PPD VRCC files.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information that might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the party responsible for collecting data from the participant will inform Pfizer immediately of any urgent safety measures taken by the party to protect the study participants against any immediate hazard, and of any serious breaches of this non-interventional study protocol that the that party becomes aware of.

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 Registry.

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

13. REFERENCES

1. Buse DC, Loder EW, Gorman JA, et al. Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache*. Sep 2013;53(8):1278-99. doi:10.1111/head.12150

2. Cassina M, Di Gianantonio E, Toldo I, Battistella PA, Clementi M. Migraine therapy during pregnancy and lactation. *Expert Opin Drug Saf*. Nov 2010;9(6):937-48. doi:10.1517/14740338.2010.505601

3. Food and Drug Administration (FDA). Postapproval Pregnancy Safety Studies Guidance for Industry Accessed September 28, 2022, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry

4. Headache Classification Committee of the International Headache Society (IHS) The International Classification of Headache Disorders, 3rd edition. *Cephalalgia*. Jan 2018;38(1):1-211. doi:10.1177/0333102417738202

5. Burch R, Rizzoli P, Loder E. The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache*. Apr 2018;58(4):496-505. doi:10.1111/head.13281

6. Frederick IO, Qiu C, Enquobahrie DA, et al. Lifetime prevalence and correlates of migraine among women in a pacific northwest pregnancy cohort study. *Headache*. Apr 2014;54(4):675-85. doi:10.1111/head.12206

7. Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M. Headache and migraine during pregnancy and puerperium: the MIGRA-study. *J Headache Pain*. Aug 2011;12(4):443-51. doi:10.1007/s10194-011-0329-1

8. Tanos V, Raad EA, Berry KE, Toney ZA. Review of migraine incidence and management in obstetrics and gynaecology. *Eur J Obstet Gynecol Reprod Biol*. Sep 2019;240:248-255. doi:10.1016/j.ejogrb.2019.07.021

9. Edvinsson L. Blockade of CGRP receptors in the intracranial vasculature: a new target in the treatment of headache. *Cephalalgia*. Aug 2004;24(8):611-22. doi:10.1111/j.1468-2982.2003.00719.x

10. Lassen LH, Haderslev PA, Jacobsen VB, Iversen HK, Sperling B, Olesen J. CGRP may play a causative role in migraine. *Cephalalgia*. Feb 2002;22(1):54-61.

11. Goadsby PJ, Edvinsson L, Ekman R. Vasoactive peptide release in the extracerebral circulation of humans during migraine headache. *Ann Neurol*. Aug 1990;28(2):183-7. doi:10.1002/ana.410280213

12. Petersen KA, Birk S, Lassen LH, et al. The CGRP-antagonist, BIBN4096BS does not affect cerebral or systemic haemodynamics in healthy volunteers. *Cephalalgia*. Feb 2005;25(2):139-47. doi:10.1111/j.1468-2982.2004.00830.x

13. Durham PL. CGRP-receptor antagonists--a fresh approach to migraine therapy? *The New England journal of medicine*. Mar 11 2004;350(11):1073-5. doi:10.1056/NEJMp048016

14. Food and Drug Administration. HIGHLIGHTS OF PRESCRIBING INFORMATION: NURTEC ODT (rimegepant) orally disintegrating tablets, for sublingual or oral use. Accessed September 28, 2022. https://biohaven-nurtec-consumer-assets.s3.amazonaws.com/nurtec-prescribing-information.pdf

15. Skajaa N, Szepligeti SK, Xue F, et al. Pregnancy, Birth, Neonatal, and Postnatal Neurological Outcomes After Pregnancy With Migraine. *Headache*. Jun 2019;59(6):869-879. doi:10.1111/head.13536

16. Aukes AM, Yurtsever FN, Boutin A, Visser MC, de Groot CJM. Associations Between Migraine and Adverse Pregnancy Outcomes: Systematic Review and Meta-analysis. *Obstet Gynecol Surv*. Dec 2019;74(12):738-748. doi:10.1097/OGX.0000000000000738

17. Chen HM, Chen SF, Chen YH, Lin HC. Increased risk of adverse pregnancy outcomes for women with migraines: a nationwide population-based study. *Cephalalgia*. Apr 2010;30(4):433-8. doi:10.1111/j.1468-2982.2009.01935.x

18. Marozio L, Facchinetti F, Allais G, et al. Headache and adverse pregnancy outcomes: a prospective study. *Eur J Obstet Gynecol Reprod Biol*. Apr 2012;161(2):140-3. doi:10.1016/j.ejogrb.2011.12.030

19. Banhidy F, Acs N, Horvath-Puho E, Czeizel AE. Pregnancy complications and delivery outcomes in pregnant women with severe migraine. *Eur J Obstet Gynecol Reprod Biol*. Oct 2007;134(2):157-63. doi:10.1016/j.ejogrb.2006.08.025

20. Facchinetti F, Allais G, Nappi RE, et al. Migraine is a risk factor for hypertensive disorders in pregnancy: a prospective cohort study. *Cephalalgia*. Mar 2009;29(3):286-92. doi:10.1111/j.1468-2982.2008.01704.x

21. Adeney KL, Williams MA, Miller RS, Frederick IO, Sorensen TK, Luthy DA. Risk of preeclampsia in relation to maternal history of migraine headaches. *J Matern Fetal Neonatal Med*. Sep 2005;18(3):167-72. doi:10.1080/14767050500260566

22. Simbar M, Karimian Z, Afrakhteh M, Akbarzadeh A, Kouchaki E. Increased risk of pre-eclampsia (PE) among women with the history of migraine. *Clin Exp Hypertens*. May 2010;32(3):159-65. doi:10.3109/10641960903254489

23. Chen YC, Tang CH, Ng K, Wang SJ. Comorbidity profiles of chronic migraine sufferers in a national database in Taiwan. *J Headache Pain*. Jun 2012;13(4):311-9. doi:10.1007/s10194-012-0447-4

24. Goulart AC, Santos IS, Brunoni AR, et al. Migraine headaches and mood/anxiety disorders in the ELSA Brazil. *Headache*. Sep 2014;54(8):1310-9. doi:10.1111/head.12397

25. Negro A, Delaruelle Z, Ivanova TA, et al. Headache and pregnancy: a systematic review. *J Headache Pain*. Oct 19 2017;18(1):106. doi:10.1186/s10194-017-0816-0

26. Bromfield EB, Dworetzky BA, Wyszynski DF, Smith CR, Baldwin EJ, Holmes LB. Valproate teratogenicity and epilepsy syndrome. *Epilepsia*. Dec 2008;49(12):2122-4. doi:10.1111/j.1528-1167.2008.01696.x

27. Hernandez-Diaz S, Huybrechts KF, Desai RJ, et al. Topiramate use early in pregnancy and the risk of oral clefts: A pregnancy cohort study. *Neurology*. Jan 23 2018;90(4):e342-e351. doi:10.1212/WNL.0000000000004857

28. Li DK, Ferber JR, Odouli R, Quesenberry C. Use of nonsteroidal antiinflammatory drugs during pregnancy and the risk of miscarriage. *Am J Obstet Gynecol*. Sep 2018;219(3):275 e1-275 e8. doi:10.1016/j.ajog.2018.06.002

29. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK. Births: Final Data for 2019. *Natl Vital Stat Rep*. Apr 2021;70(2):1-51.

30. Eshera N, Itana H, Zhang L, Soon G, Fadiran EO. Demographics of clinical trials participants in pivotal clinical trials for new molecular entity drugs and biologics approved by FDA From 2010 to 2012. *Am J Ther*. Nov-Dec 2015;22(6):435-55. doi:10.1097/MJT.0000000000000177

31. Food and Drug Administration. Clinical Trial Diversity. Accessed December 6, 2021. https://www.fda.gov/consumers/minority-health-and-health-equity/clinical-trial-diversity

32. Cohen LS, Goez-Mogollon L, Sosinsky AZ, et al. Risk of Major Malformations in Infants Following First-Trimester Exposure to Quetiapine. *Am J Psychiatry*. Dec 1 2018;175(12):1225-1231. doi:10.1176/appi.ajp.2018.18010098

33. Hernandez-Diaz S, McElrath TF, Pennell PB, et al. Fetal growth and premature delivery in pregnant women on antiepileptic drugs. *Ann Neurol*. Sep 2017;82(3):457-465. doi:10.1002/ana.25031

34. Sinclair SM, Jones JK, Miller RK, Greene MF, Kwo PY, Maddrey WC. The Ribavirin Pregnancy Registry: An Interim Analysis of Potential Teratogenicity at the Mid-Point of Enrollment. *Drug Saf*. Dec 2017;40(12):1205-1218. doi:10.1007/s40264-017-0566-6

35. Ford JH, Foster SA, Nichols RM, et al. A real-world analysis of patient-reported outcomes in patients with migraine by preventive treatment eligibility status in the US and Europe. *J Patient Rep Outcomes*. Jul 6 2020;4(1):53. doi:10.1186/s41687-020-00221-w

36. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, Benedetto C. Gender-related differences in migraine. *Neurol Sci*. Dec 2020;41(Suppl 2):429-436. doi:10.1007/s10072-020-04643-8

37. Stewart WF, Lipton RB, Liberman J. Variation in migraine prevalence by race. *Neurology*. Jul 1996;47(1):52-9. doi:10.1212/wnl.47.1.52

38. ConcePTION. Description: Key objectives of the project. Accessed September 28, 2022, https://www.imi-conception.eu/background/description/

39. Dudman DC, Tauqeer F, Kaur M, Ritchey ME, Li H, Lopez-Leon S. A systematic review and meta-analyses on the prevalence of pregnancy outcomes in migraine treated patients: a contribution from the IMI2 ConcePTION project. *J Neurol*. Feb 2022;269(2):742-749. doi:10.1007/s00415-021-10534-5

40. US Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities. CDC/BPA 6-digit code for Congenital Anomalies. Accessed September 28, 2022, https://www.cdc.gov/ncbddd/birthdefects/macdp.html#CaseDefinition

41. European Surveillance of Congenital Anomalies (EUROCAT). EUROCAT Guide 1.4 and Reference Documents. 2021;

42. Holmes LB, Westgate MN. Inclusion and exclusion criteria for malformations in newborn infants exposed to potential teratogens. *Birth Defects Res A Clin Mol Teratol*. Sep 2011;91(9):807-12. doi:10.1002/bdra.20842

43. Reller MD, Strickland MJ, Riehle-Colarusso T, Mahle WT, Correa A. Prevalence of congenital heart defects in metropolitan Atlanta, 1998-2005. *J Pediatr*. Dec 2008;153(6):807-13. doi:10.1016/j.jpeds.2008.05.059

44. European Surveillance of Congenital Anomalies (EUROCAT). EUROCAT Guide 1.4 and Reference Documents. Accessed September 28, 2022. https://eu-rd-platform.jrc.ec.europa.eu/sites/default/files/Full_Guide_1_4_version_28_DEC2018.pdf

45. (CDC) CfDCaP. High blood pressure during pregnancy. 2020.

46. Bulletins--Obstetrics ACoP. ACOG practice bulletin. Diagnosis and management of preeclampsia and eclampsia. Number 33, January 2002. *Obstet Gynecol*. Jan 2002;99(1):159-67. doi:10.1016/s0029-7844(01)01747-1

47. American Diabetes A. Gestational diabetes mellitus. *Diabetes Care*. Jan 2004;27 Suppl 1:S88-90. doi:10.2337/diacare.27.2007.s88

48. Villar J, Cheikh Ismail L, Victora CG, et al. International standards for newborn weight, length, and head circumference by gestational age and sex: the Newborn Cross-Sectional Study of the INTERGROWTH-21st Project. *Lancet*. Sep 6 2014;384(9946):857-68. doi:10.1016/S0140-6736(14)60932-6

49. Villar J, Giuliani F, Fenton TR, et al. INTERGROWTH-21st very preterm size at birth reference charts. *Lancet*. Feb 27 2016;387(10021):844-5. doi:10.1016/S0140-6736(16)00384-6

50. US Centers for Disease Control and Prevention (CDC), National Center for Health Statistics. Clinical Growth Charts. Accessed September 28, 2022, https://www.cdc.gov/growthcharts/clinical_charts.htm

51. US Centers for Disease Control and Prevention (CDC). Understanding Children's Developmental Milestones. Accessed September 28, 2022, https://www.cdc.gov/ncbddd/childdevelopment/screening.html

52. (AAP) AAoP. Recommendations for Preventive Pediatric Health Care. Accessed September 28, 2022, https://downloads.aap.org/AAP/PDF/periodicity_schedule.pdf

53. Scheuerle A, Tilson H. Birth defect classification by organ system: a novel approach to heighten teratogenic signalling in a pregnancy registry. *Pharmacoepidemiol Drug Saf*. Sep 2002;11(6):465-75. doi:10.1002/pds.726

54. US Centers for Disease Control and Prevention (CDC), National Center on Birth Defects and Developmental Disabilities. Update on overall prevalence of major birth defects--Atlanta, Georgia, 1978-2005. *MMWR Morbidity and mortality weekly report*. 2008;57(1):1-5.

55. Gelperin K, Hammad H, Leishear K, et al. A systematic review of pregnancy exposure registries: examination of protocol-specified pregnancy outcomes, target sample size, and comparator selection. *Pharmacoepidemiol Drug Saf*. Feb 2017;26(2):208-214. doi:10.1002/pds.4150

56. Covington DL MH, Churchill P, et al. Improving accuracy in enrollment targets for pregnancy registries. *Pharmacoepidemiol Drug Saf*. 2010;19(1):S71-72.

57. Veley K CD, Buus R, Chan RL, Churchill P. Sample size calculations for pregnancy. *Pharmacoepidemiol Drug Saf*. 2020;29(3):537-538.

58. Covington DL VK, Buus R, et al. Factors associated with losses to follow-up in pregnancy exposure registries. presented at: 36th International Conference for Pharmacoepidemiology; September 16-17, 2020 2020;

59. Correa A, Cragan JD, Kucik JE, et al. Reporting birth defects surveillance data 1968-2003. *Birth Defects Res A Clin Mol Teratol*. Feb 2007;79(2):65-186. doi:10.1002/bdra.20350

60. Soe M, Sullivan K. Open Source Epidemiologic Statistics for Public Health (OpenEpi). Accessed April 7, 2021, https://www.openepi.com/Power/PowerCohort.htm

61. Butwick AJ, Druzin ML, Shaw GM, Guo N. Evaluation of US State-Level Variation in Hypertensive Disorders of Pregnancy. *JAMA Netw Open*. Oct 1 2020;3(10):e2018741. doi:10.1001/jamanetworkopen.2020.18741

62. Ananth CV, Keyes KM, Wapner RJ. Pre-eclampsia rates in the United States, 1980-2010: age-period-cohort analysis. *BMJ*. Nov 7 2013;347:f6564. doi:10.1136/bmj.f6564

63. Wu P, Velez Edwards DR, Gorrindo P, et al. Association between First Trimester Antidepressant Use and Risk of Spontaneous Abortion. *Pharmacotherapy*. Sep 2019;39(9):889-898. doi:10.1002/phar.2308

64. MacDorman MF, Gregory EC. Fetal and Perinatal Mortality: United States, 2013. *Natl Vital Stat Rep*. Jul 23 2015;64(8):1-24.

65. Jatlaoui TC, Eckhaus L, Mandel MG, et al. Abortion Surveillance - United States, 2016. *MMWR Surveill Summ*. Nov 29 2019;68(11):1-41. doi:10.15585/mmwr.ss6811a1

66. Khoshnood B, Greenlees R, Loane M, Dolk H, Committee EPM, Group EW. Paper 2: EUROCAT public health indicators for congenital anomalies in Europe. *Birth Defects Res A Clin Mol Teratol*. Mar 2011;91 Suppl 1:S16-22. doi:10.1002/bdra.20776

67. Mason CA, Kirby RS, Sever LE, Langlois PH. Prevalence is the preferred measure of frequency of birth defects. *Birth Defects Res A Clin Mol Teratol*. Oct 2005;73(10):690-2. doi:10.1002/bdra.20211

68. Robins JM, Rotnitzky A, Zhao LP. Estimation of regression coefficients when some regressors are not always observed. *Journal of the American Statistical Association*. 1994;89(427):846-866.

69. Robins JM, Rotnitzky A. Semiparametric efficiency in multivariate regression models with missing data. *Journal of the American Statistical Association*. 1995;90(429):122-129.

70. Scharfstein DO, Rotnitzky A, Robins JM. Adjusting for Nonignorable Drop-Out Using Semiparametric Nonresponse Models. *Journal of the American Statistical Association*. 1999;94(448):1096-1120.

71. Gliklich RE, Dreyer NA, Leavy MB. Registries for evaluating patient outcomes: a user's guide. 2014;

72. Polifka JE, Friedman JM. Medical genetics: 1. Clinical teratology in the age of genomics. *CMAJ*. Aug 6 2002;167(3):265-73.

73. Feldkamp ML, Botto LD, Carey JC. Reflections on the etiology of structural birth defects: Established teratogens and risk factors. *Birth Defects Res A Clin Mol Teratol*. Aug 2015;103(8):652-5. doi:10.1002/bdra.23392

74. TERIS. TERIS: the Teratogen Information System. Accessed September 28, 2022, https://terisdb.deohs.washington.edu/Teris/Teris1a.aspxReturnUrl=%2fteris%2fdefault.aspx.

75. Kennedy DL, Uhl K, Kweder SL. Pregnancy exposure registries. *Drug Saf*. 2004;27(4):215-28. doi:10.2165/00002018-200427040-00001

76. Ispe. Guidelines for good pharmacoepidemiology practices (GPP). *Pharmacoepidemiol Drug Saf*. Feb 2008;17(2):200-8. doi:10.1002/pds.1471

77. Eltonsy S, Martin B, Ferreira E, Blais L. Systematic procedure for the classification of proven and potential teratogens for use in research. *Birth Defects Res A Clin Mol Teratol*. Apr 2016;106(4):285-97. doi:10.1002/bdra.23491

78. TERIS. Website. Teratogen Information System; Department of Environmental and Occupational Health Sciences, School of Public Health, University of Washington. Accessed September 28, 2022, https://deohs.washington.edu/teris/

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15. LIST OF FIGURES

None

16. ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

17. ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study 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)

EU PAS Register® number: EUPAS45356
Study reference number (if applicable): C4951005 (formerly BHV3000-402)

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

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

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
2.1.2 The objective(s) of the study?	☒	☐	☐	8.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.1/9.7.3.3
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.3.1
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	9.2
4.2.2 Age and sex	☒	☐	☐	9.2
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.1/9.2.2

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3/9.9
5.3 Is exposure categorized according to time windows?	☒	☐	☐	9.3.3/9.4.3
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.3/9.4.3
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.3
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.3.2/ 9.3.3.3

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.3.4

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.4/ 9.7.3.3
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.9
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☐	☒	

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.7.3.4/ 9.7.3.5/ 9.7.3.6/ 9.7.3.7
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.9
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3.1/ 9.7.3.5/ 9.7.3.6/ 9.9

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.7.3.5/ 9.7.3.7

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4.1/ 9.4.3
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4.1/ 9.4.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4.1/ 9.4.5
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4.1/ 9.4.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4.1/ 9.4.4
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4.1/ 9.4.5
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.6.1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.6.1/9.4.4
9.3.3 Covariates and other characteristics?	☒	☐	☐	9.6.1
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7, 9.7.2
10.4 Are stratified analyses included?	☒	☐	☐	9.7.3.5
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.3.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.3.5/ 9.7.3.6/ 9.7.3.7/ 9.9
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.3.7

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.3.4.1/ 9.4.4/ 9.8.2

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.7.3.4/ 9.9
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.4
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	10.4
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author(s) of the protocol: Kristin Veley

Date: 25/Apr/2023

Signature:

DocuSigned by:
Kristin Veley
Signer Name: Kristin Veley
Signing Reason: I approve this document
Signing Time: 25-Apr-2023 | 4:46:50 PM GMT
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18. ANNEX 3. LIST OF MIGRAINE THERAPIES

Table 6 provides a list of other migraine therapies. Please note, combination products of products already listed are not included.

Table 6. List of Migraine Therapies

Drug class	Generic name
Triptans	Almotriptan
	Eletriptan
	Frovatriptan
	Naratriptan
	Rizatriptan
	Sumatriptan
	Zolmitriptan
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
Anti-depressants	Nefazodone
	Bupropion
	Amitriptyline

Drug class	Generic name
	Trazodone
	Nortriptyline
	Sertraline
	Fluoxetine
	Paroxetine
	Duloxetine
	Venlafaxine
Beta-blockers	Atenolol
	Bisoprolol
	Carvedilol
	Esmolol
	Labetalol
	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

Drug class	Generic name
	Botulinum toxin type B
Ergotamine	Dihydroergotamine
	Ergotamine
CGRP inhibitors (with the exception of rimegepant, exposure to these agents is criteria for exclusion)	Fremanezumab
	Erenumab
	Galcanezumab
	Ubrogepant
	Zavegepant
	Rimegepant
Ditans (exposure to these agents is criteria for exclusion)	Lasmiditan
Complementary medications	Butterbur (petasites)
	Feverfew (MIG-99)
	Caffeine

CGRP = calcitonin gene-related peptide

19. ANNEX 4. LIST OF KNOWN TERATOGENS

Table 7 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[72-74].

Table 7. List of Known Teratogens

Drug class/generic name	Half-life	Relevant exposure window[a]
Androgens		
Methyltestosterone	6 to 8 h	First, second, and third trimesters
Testosterone	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 d.	First, second, and third trimesters
Mesterolone	12 to 13 h	Not in TERIS. Assumed window: first, second, and third trimesters
Nandrolone	144 to 288 h	Unknown. Assumed window: first, second, and third trimesters
Oxandrolone	13.3 h	Unknown. Assumed window: first, second, and third trimesters
Prasterone	12 h	Unknown. Assumed window: first, second, and third trimesters
Fluoxymesterone	9.2 h	Unknown. Assumed window: first, second, and third trimesters
Angiotensin II receptor antagonists		
Candesartan	9 h	First, second, and third trimesters
Eprosartan	20 h	First, second, and third trimesters
Irbesartan	11 to 15 h	First, second, and third trimesters
Losartan	2 h	First, second, and third trimesters
Olmesartan	13 h	First, second, and third trimesters
Tasosartan	Not available, but half-life of angiotensin II receptor antagonists ranges from 1 to 3 d	First, second, and third trimesters
Telmisartan	24 h	First, second, and third trimesters
Valsartan	6 h	First, second, and third trimesters
Angiotensin-converting enzyme inhibitors		
Benazepril	10 to 11 h	First, second, and third trimesters

Drug class/generic name	Half-life	Relevant exposure window[a]
Captopril	2 h	First, second, and third trimesters
Cilazapril	9 h	First, second, and third trimesters
Enalapril	11 h	First, second, and third trimesters
Fosinopril	11.5 to 14 h	First, second, and third trimesters
Lisinopril	12 h	First, second, and third trimesters
Moexipril	12 h	First, second, and third trimesters
Perindopril	0.8 to 1 h	First, second, and third trimesters
Quinapril	3 h	First, second, and third trimesters
Ramipril	13 to 17 h	First, second, and third trimesters
Trandolapril	6 h	First, second, and third trimesters
Anti-arrhythmics		
Amiodarone	61 d	First, second, and third trimesters
Antibiotics		
Sulfamethoxazole/ Trimethoprim	8 to 10 h	3 months before conception and first trimester for MCMs and second trimester for preterm birth and low birth weight
Anticoagulants		
Acenocoumarol	8 to 11 h	First, second, and third trimesters
Dicumarol	1 to 2 d	At least 2 weeks before conception and first, second, and third trimesters
Phenprocoumon	4 to 6 d	First, second, and third trimesters
Warfarin	40 h	At least 2 weeks before conception and first, second, and third trimesters
Anti-epileptics		
Lamotrigine	Adult, 25.4 to 70.3 h (healthy volunteers); 12.6 to 58.8 h (epilepsy)	First, second, and third trimesters
Trimethadione/ Paramethadione	Paramethadione—12 to 24 h Trimethadione—11 to 16 h	First, second, and third trimesters
Valproic Acid, Valproate	9 to 16 h	Primarily first trimester, but MCMs have been associated with second and third trimester exposures
Carbamazepine	12 to 65 h	First, second, and third trimesters
Ethotoin	3 to 9 h	First, second, and third trimesters
Phenytoin, fosphenytoin	Phenytoin: 7 to 42 h Fosphenytoin: 15 min	First, second, and third trimesters
Primidone	10 h	First, second, and third trimesters

Drug class/generic name	Half-life	Relevant exposure window[a]
Topiramate	21 h	First, second, and third trimesters
Ethosuximide	17 to 56 h	Unknown. Assumed window: first, second, and third trimesters
Oxcarbazepine	Oxcarbazepine: immediate-release formulations, about 2 h; extended-release tablet, 7 to 11 h Active metabolite, 10–monohydroxy: 9 to 11 h	Unknown. Assumed window: first, second, and third trimesters
Sulthiame	24 h	Not in TERIS. Assumed window: first, second, and third trimesters
Vigabatrin	10.5 h	Unknown. Assumed window: first, second, and third trimesters
Phenobarbital	70 to 140 h	First, second, and third trimesters
Methylphenobarbital	34 h	Unknown. Assumed window: first, second, and third trimesters
Antifungals		
Fluconazole	30 h	2 weeks before conception and first trimester
Flucytosine	2.4 to 4.8 h	First trimester
Antineoplastics		
Aminopterin	12 to 24 h	First, second, and third trimesters
Asparaginase	5.7 d	3 months before conception and first, second, and third trimesters
Axitinib	2.5 to 6.1 h	1 week before conception and first, second, and third trimesters
Brentuximab vedotin	4 to 6 d	6 months before conception and first, second, and third trimesters
Methotrexate	55 h	6 months before conception and first, second, and third trimesters
Crizotinib	42 h	45 days before conception and first, second, and third trimesters
Cytarabine	1 to 3 h	6 months before conception and first, second, and third trimesters

Drug class/generic name	Half-life	Relevant exposure window[a]
Daunorubicin	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	6 months before conception and first, second, and third trimesters
Exemestane	24 h	1 month before conception and first, second, and third trimesters
Mechlorethamine	15 min	First, second, and third trimesters
Mercaptopurine	10 h	6 months before conception and first, second, and third trimesters.
Vinblastine	24.8 h	First, second, and third trimesters
Cyclophosphamide	3 to 12 h	12 months before conception and first trimester
Altretamine	4.7 to 10.2 h	Unknown. Assumed window: first, second, and third trimesters
Amsacrine	8 to 9 h	3 months before conception and first, second, and third trimesters
Bevacizumab	480 h	6 months before conception and first, second, and third trimesters
Bleomycin	2 h	Unknown. Assumed window: first, second, and third trimesters
Bortezomib	40 to 193 h	7 months before conception and first, second, and third trimesters
Busulfan	2.3 to 3.4 h	6 months before conception and first, second, and third trimesters
Capecitabine	0.75 h	6 months before conception and first, second, and third trimesters
Carboplatin	2.6 to 5.9 h	Not in TERIS. Assumed window: first, second, and third trimesters
Carmustine	IV, 15 to 75 min	3 months before conception and first, second, and third trimesters
Cetuximab	63 to 230 h	2 months before conception and first, second, and third trimesters
Chlorambucil	1.5 h	Not in TERIS. Assumed window: first, second, and third trimesters
Cisplatin	20 to 30 min	14 months before conception and first, second, and third trimesters

Drug class/generic name	Half-life	Relevant exposure window[a]
Cladribine	1 d	6 months before conception and first, second, and third trimesters
Clofarabine	5.2 h	6 months before conception and first, second, and third trimesters
Dacarbazine	5 h	Unknown. Assumed window: first, second, and third trimesters
Dactinomycin	36 h	6 months before conception and first, second, and third trimesters
Dasatinib	3 to 5 h	Unknown. Assumed window: first, second, and third trimesters
Docetaxel	11.1 h	6 months before conception and first, second, and third trimesters
Doxorubicin	20 to 48 h	6 months before conception and first, second, and third trimesters
Epirubicin	31.1 h +/- 6 h to 35.3 h +/− 9 h	6 months before conception and first, second, and third trimesters
Erlotinib	36.2 h	2 weeks before conception and first, second, and third trimesters
Estramustine	10 to 20 h	Not in TERIS. Assumed window: first, second, and third trimesters
Etoposide	4 to 11 h	6 months before conception and first, second, and third trimesters
Fludarabine	20 h	6 months before conception and first, second, and third trimesters
Fluorouracil	8 to 20 min	3 months before conception and first, second, and third trimesters
Gemcitabine	1.7 to 19.4 h	6 months before conception and first, second, and third trimesters
Hydroxycarbamide	2 to 4.5 h	Unknown. Assumed window: first, second, and third trimesters
Idarubicin	20 to 22 h	6.5 months before conception and first, second, and third trimesters
Ifosfamide	15 h	Unknown. Assumed window: first, second, and third trimesters
Imatinib	18 h	2 weeks before conception and first, second, and third trimesters
Irinotecan	6 to 12 h	6 months before conception and first, second, and third trimesters
Lapatinib	24 h	1 week before conception and first, second, and third trimesters

Drug class/generic name	Half-life	Relevant exposure window[a]
Lomustine	16 to 48 h	2 weeks before conception and first, second, and third trimesters
Melphalan	10 to 75 min	Unknown. Assumed window: first, second, and third trimesters
Mitomycin	46 min	6 months before conception and first, second, and third trimesters
Mitoxantrone	23 to 215 h	Not in TERIS. Assumed window: first, second, and third trimesters
Nelarabine	Adults: prodrug: 30 min; ara-G: 3 h	Unknown. Assumed window: first, second, and third trimesters
Oxaliplatin	392 h	9 months before conception and first, second, and third trimesters
Paclitaxel	13 to 52 h	6 months before conception and first, second, and third trimesters
Pemetrexed	3.5 h	6 months before conception and first, second, and third trimesters
Pembrolizumab	22 d	4 months before conception and first, second, and third trimesters
Pentostatin	5.7 h	Not in TERIS. Assumed window: first, second, and third trimesters
Procarbazine	IV, approximately 10 min	Not in TERIS. Assumed window: first, second, and third trimesters
Raltitrexed	260 h	6 months before conception and first, second, and third trimesters
Sorafenib	25 to 48 h	6 months before conception and first, second, and third trimesters
Streptozocin	Systemic: 35 min unchanged drug; 40 h metabolites	1 months before conception and first, second, and third trimesters
Sunitinib	40 to 60 h	1 month before conception and first, second, and third trimesters
Tegafur	6.7 to 11.3 h	6 months before conception and first, second, and third trimesters
Temozolomide	1.8 h	6 months before conception and first, second, and third trimesters
Teniposide	5 h	Not in TERIS. Assumed window: first, second, and third trimesters
Thioguanine	80 min	Not in TERIS. Assumed window: first, second, and third trimesters
Thiotepa	1.4 to 3.7 h	6 months before conception and first, second, and third trimesters

Drug class/generic name	Half-life	Relevant exposure window[a]
Topotecan	2 to 3 h	6 months before conception and first, second, and third trimesters
Vincristine	85 h	Unknown. Assumed window: first, second, and third trimesters
Vindesine	2.9 h	Not in TERIS. Assumed window: first, second, and third trimesters
Vinorelbine	27.7 to 43.6 h	6 months before conception and first, second, and third trimesters
Lenalidomide	3 h	4 weeks before conception and first, second, and third trimesters
Antithyroid		
Propylthiouracil	1 to 2 h	First and second trimesters
Methimazole	4.9 to 5.7 h	First, second, and third trimesters
Radioiodine	192 h	6-12 months before conception and first, second, and third trimesters
Antivirals		
Ribavirin	12 d	6 months before conception and first, second, and third trimesters
Estrogens		
Diethylstilbestrol	Diethylstilbestrol reaches peak concentration within 20 to 40 min, having a primary half-life of 3 to 6 h. It has a terminal half-life of 2 to 3 d due to entero-hepatic circulation	First, second, and third trimesters
Immunomodulatory agents		
Mycophenolate mofetil	16 h	First, second, and third trimesters
Thalidomide	5 to 7 h	1 month before conception and first, second, and third trimesters
Penicillamine	2 to 4 h	First, second, and third trimesters
Azathioprine	5 h	Primarily first trimester, but other outcomes have been associated with exposures “during pregnancy”
Leflunomide	432 to 456 h	2 years before conception and first, second, and third trimesters
Mycophenolic acid	8 to 16 h	Primarily first trimester, but other outcomes have been associated with exposures “during pregnancy”
Mood stabilizer		
Lithium	24 h	First, second, and third trimesters

Drug class/generic name	Half-life	Relevant exposure window[a]
NSAIDs		
Indomethacin	4.5 h	Second and third trimesters; unlikely risk associated with first trimester exposure
Prostaglandin analogues		
Misoprostol	20 to 40 min	1 month before conception and first, second, and third trimesters
Retinoids		
Alitretinoin	9 h	1 month before conception and first, second, and third trimesters
Tretinoin	0.5 to 2 h	Unknown. Assumed window: first, second, and third trimesters
Vitamin A	TERIS only notes "long half-life"	Doses above 10,000 IU/day may be teratogenic: First, second, and third trimesters
Acitretin	acitretin: 33 to 96 h cis-acitretin: 28 to 157 h	3 years before conception and throughout pregnancy, especially first trimester
Etretinate	120 d to 3 y	3 years before conception and throughout pregnancy, especially first trimester
Isotretinoin	10 to 12 h	1 month before conception and first, second, and third trimesters
Tazarotene	18 h	First, second, and third trimesters
Retinol	2 to 9 h	12 months before conception and first trimester
Steroids		
Danazol	9.7 to 23.7 h	First, second, and third trimesters
Tetracyclines		
Demeclocycline	10 to 17 h	Second and third trimesters
Oxytetracycline	6 to 11 h	Second and third trimesters
Tetracycline	6 to 11 h	Second and third trimesters; limited data for first trimester exposure
Chlortetracycline	5.6 h	Unknown. Assumed window: second and third trimesters
Doxycycline	18 to 22 h	Unknown. Assumed window: second and third trimesters
Methacycline	14 to 22 h	Unknown. Assumed window: second and third trimesters

Drug class/generic name	Half-life	Relevant exposure window[a]
Minocycline	11 to 24.31 h	Unknown. Assumed window: second and third trimesters
Tigecycline	27 to 43 h	Unknown. Assumed window: second and third trimesters

d = day; h = hour; IV = intravenous; MCM = major congenital malformation; min = minute; NSAIDs = nonsteroidal anti-inflammatory drugs; TERIS = Teratogen Information System; y = year.
Sources: Eltonsy, Martin, Ferreira and Blais [77]; TERIS [78]; DrugBank online available at https://go.drugbank.com; product labels, which are available at: https://www.accessdata.fda.gov/scripts/cder/daf/ and https://dailymed.nlm.nih.gov/dailymed/index.cfm; summary of product characteristics at https://www.ema.europa.eu/en/medicines and https://products.mhra.gov.uk/; and product monographs at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.

[a] Teratogens with unknown relevant exposure windows will be assigned an exposure window equivalent to other product(s) in the same class.