NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	Retrospective Cohort Study of Pregnancy Outcomes in Women Exposed to Rimegepant During Pregnancy
Protocol number	C4951006 (formerly BHV3000-403)
Protocol version identifier	V5.0
Date	21-Aug-2023
ClinicalTrials.gov identifier	NCT05198245
EU Post Authorization Study (PAS) register number	EUPAS45952
Active substance	Rimegepant (formerly BHV-3000), ATC code N02CD06
Medicinal product	Nurtec ODT®/Vydura®
Product reference	PF-07899801 (US) EU/1/22/1645 (EU)
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	The primary research question of this study is, Is there an increased risk of adverse fetal, maternal, and infant outcomes in women with migraine exposed to rimegepant during pregnancy? The primary objective is to evaluate the risk of pregnancy and infant outcomes with major congenital malformations (MCMs) as

	the primary outcome of interest, and other primary outcomes including spontaneous abortions, fetal deaths/stillbirths, and small-for-gestational-age (SGA) births among women with migraine exposed to rimegepant during pregnancy and in 2 rimegepant-unexposed comparator groups. Specific objectives are to describe patterns of use of rimegepant in pregnant women; to estimate the frequency of pregnancy outcomes (i.e., spontaneous abortions, fetal death/stillbirths, and elective terminations), pregnancy complications (pre-eclampsia/eclampsia), and fetal/infant outcomes (i.e., MCMs, SGA births, and preterm births) in women who used rimegepant and in 2 unexposed comparator groups; to estimate the adjusted relative risks (RRs) for the study outcomes among women exposed to rimegepant in pregnancy compared with each of the 2 unexposed comparator groups.
Country(-ies) of study	United States
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Marketing Authorization Holder(s)

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
AEM	Adverse event monitoring
CGRP	Calcitonin gene–related peptide
CI	Confidence interval
CMV	Cytomegalovirus
CPT	Current Procedural Terminology
DAPI	Dynamic Assessment of Pregnancies and Infants
ED	Emergency department
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union Electronic Register of Post-Authorisation Studies
EUROCAT	European Surveillance of Congenital Anomalies programme
FDA	Food and Drug Administration
GP	General practitioner
HCPCS	Healthcare Common Procedure Coding System
ICD	*International Classification of Diseases*
ICD-10	*International Statistical Classification of Diseases, 10th Revision*
ICD-10-CM	*International Classification of Diseases, 10th Revision, Clinical Modification*
ICD-9	*International Classification of Diseases, 9th Revision*

ICD-9-CM	*International Classification of Diseases, 9th Revision, Clinical Modification*
IEC	Independent ethics committee
IRB	Institutional review board
ISPE	International Society for Pharmacoepidemiology
LMP	First day of the last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MAH	Marketing authorization holder
MCM	Major congenital malformation
NIS	Non-interventional study
NSAID	Nonsteroidal anti-inflammatory drug
ODT	Orally disintegrating tablet
OR	Odds ratio
ORD	Optum Research Database
PASS	Postauthorization safety study
PPV	Positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
Q*n*	Quarter of the calendar year
QC	Quality control
RR	Relative risk
RTI-HS	RTI Health Solutions
SAP	Statistical analysis plan
SARS-COV-2	Severe acute respiratory syndrome coronavirus 2
SGA	Small for gestational age

SOP	Standard operating procedure
TERIS	Teratogen Information System
TORCH infections	Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), herpes simplex, and Zika virus disease
US	United States
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job title	Affiliation	Address
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4. ABSTRACT

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

Version 5.0

Authors: Elena Rivero, Andrea Margulis, RTI Health Solutions

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

Pfizer (and formerly Biohaven) is committed to fulfilling a postmarketing requirement by the FDA Center for Drug Evaluation and Research to conduct a pregnancy outcomes study using claims or electronic medical record data with outcome validation to assess MCMs, spontaneous abortions, stillbirths, and SGA births in women exposed to rimegepant during pregnancy relative to an unexposed comparator population. The study will include 2 unexposed comparator groups: 1 of pregnant women with migraine and another without migraine. Additionally, other outcomes of pregnancy and maternal complications of pregnancy for which there is evidence of increased risk associated with some migraine therapies or with migraine will be included as secondary study outcomes. This study is also part of the European Union (EU) risk management plan for Vydura® (rimegepant), included as a Category 3 postauthorization safety study, which aims to provide information to address the safety concern of "missing information" on the use of rimegepant in pregnant women.

Research question and objectives: The primary research question of this study is, Is there an increased risk of adverse fetal, maternal, and infant outcomes in women with migraine exposed to rimegepant during pregnancy?

The primary objective is to evaluate the risk of pregnancy and infant outcomes with MCMs as the primary outcome of interest, and other primary outcomes including spontaneous abortions, fetal deaths/stillbirths, and SGA births among women with migraine exposed to rimegepant during pregnancy[1] and in 2 rimegepant-unexposed comparator groups. Specific objectives are as follows:

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

[1] See Table 10 for the relevant exposure window for each study outcome. The primary analysis will assess the association between first trimester rimegepant exposure and risk of MCMs.

- Objective 2: To estimate the frequency of pregnancy outcomes (i.e., spontaneous abortions, fetal deaths/stillbirths, elective terminations), complications of pregnancy (i.e., pre-eclampsia/eclampsia), and fetal/infant outcomes (i.e., MCMs, SGA births, and preterm births) in women with migraine exposed to rimegepant during pregnancy and in 2 comparator groups of pregnant women not exposed to rimegepant
- Objective 3: To estimate the adjusted relative risks (RRs) for the study outcomes among women exposed to rimegepant in pregnancy compared with the unexposed comparator groups

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

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

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

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

- Had a pregnancy code or a recorded pregnancy outcome (i.e., live birth, stillbirth, spontaneous abortion, or elective termination) within the study period
- Be aged 16 to 49 years, inclusive, at the estimated LMP within the study observation period.

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

Exposure: The exposure window for rimegepant will include a 30-day period before the estimated LMP until the end of pregnancy for end-of-pregnancy and infant outcomes. During the monitoring phase, the length of the exposure period before the estimated LMP will be estimated based on the calculated median number of days between consecutive dispensings recorded within a 6-month period before the estimated LMP among all pregnant women with rimegepant dispensings (hereafter "median interval") in order to confirm whether the 30-day period before LMP is adequate or requires adjustment in the final analyses. If an adjustment is required, for each rimegepant-exposed pregnant woman, the estimated exposure window for rimegepant will start 1 median interval (days) before the estimated LMP and will end at the end of pregnancy. A pregnancy will be considered exposed to rimegepant if 1 or more pharmacy dispensings occurred within this period. For the analyses on MCMs, the exposure window will include the defined time before the estimated LMP until the end of the first trimester of pregnancy (see Table 10).

Similarly, for other medications indicated for the acute or preventive treatment of migraine, the exposure window will include a period before the estimated LMP that will be 30 days, except for botulinum toxin, for which the exposure period before the estimated LMP will be 90 days. This period will be evaluated annually during the monitoring phase to determine the need to adjust it to a period based on the median number of days between consecutive dispensings of each type of medication (by medication category). Additionally, information obtained through a patient survey (see Annex 4) to be conducted in a sample of women of childbearing age who are users of rimegepant or other migraine medications will be used to validate the proposed approach to estimate the time window of exposure before the estimated LMP. This survey will be conducted after approximately 2 years of availability of rimegepant for preventive treatment of migraine in the US. This period will allow for a relatively large number of users and a well-established use of rimegepant for acute and preventive treatment.

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

Study outcomes:

The primary outcome of interest is:

- MCMs

Other primary outcomes are the following:

- Spontaneous abortions
- Fetal deaths/stillbirths
- SGA births

The secondary outcomes are the following:

- Elective terminations
- Pre-eclampsia or eclampsia (combined), during pregnancy and through the postpartum period
- Preterm births

Other variables (maternal characteristics) are listed below:

- Demographics, duration of health plan enrollment before pregnancy, calendar year of pregnancy, geographic region
- Prior history of medical conditions
- Migraine type, as available
- Maternal obstetric history, as available
- Use of medications from 6 months before the estimated LMP and during pregnancy, including medications for the treatment of chronic comorbidities, and acute and preventive migraine medications
- Health care utilization
- Characteristics of current pregnancy

Data source: The patients included in this study will be drawn from the Optum Research Database (ORD), a proprietary research database that contains the eligibility data, medical claims, and pharmacy claims from a large, commercial health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US and comprise approximately 3% to 4% of the US population. This study will employ the Optum Dynamic Assessment of Pregnancies and Infants, a proprietary process that includes a set of capabilities and established algorithms that is applied to claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link mother and infant data in an ongoing manner within the ORD. Optum Dynamic Assessment of Pregnancies and Infants links health data between women and their infants through a family identifier and by matching the dates of delivery and the infant's birth. Optum can (with appropriate approvals) access medical records for a subset of mothers or infants to ascertain covariate information, to confirm outcomes and, if needed, validate algorithms for outcome ascertainment.

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

Data analysis: For Objective 1, an analysis of the use of rimegepant and other medications indicated for treatment of migraine will be conducted annually, including the number of users, and mean, standard deviation, median, interquartile range of the number of dispensings, and the number of days between consecutive dispensings for each medication (by medication category); distribution of pregnancies exposed to migraine medications in various pre-pregnancy and pregnancy periods; distribution of pregnancies exposed to rimegepant by potential acute, preventive, acute and preventive, or indeterminate treatment indication; and distribution of pregnancies in the rimegepant-exposed and the primary comparator group by type of exposure to migraine medications before and during pregnancy (i.e., exposure to acute migraine medications only, preventive migraine

medications only, and both acute and preventive migraine medications). Results will be reported for each study group in the annual interim and final reports.

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

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

The number of pregnancies will be considered when determining which analyses can be conducted. The ability to match on propensity score is contingent on the available study size. Alternatively, a weighting method on the propensity score can be applied using inverse probability of treatment weights, or the propensity score can be applied as a covariate in multivariate regression models or as a stratification variable. Inverse probability of treatment weighting will be the first alternative method to explore whether propensity score matching appears not to be feasible or appropriate.

Comparative analyses for the primary and secondary outcomes will be conducted in the final study groups when the target study size has been attained, and results will be reported in the final study report. Regression models will be used to compare pregnant women with migraine exposed to rimegepant during pregnancy with women in the primary comparator group and the secondary comparator group. Point estimates and 95% confidence intervals (CIs) from crude analyses within the matched study groups will be presented.

Milestones:

Approvals by data protection, data custodian, ethics, and scientific review bodies are complete.

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

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

5. AMENDMENTS AND UPDATES

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
V5.0	21-Aug-2023	Section 9.2.1.1, Identification of Pregnancies; Section 9.7.2, Descriptive Analyses	Updated the description of the process for pregnancy identification with the inclusion of language regarding the verification of time between multiple pregnancy episodes in a woman. Added a descriptive analysis of the time between consecutive pregnancy episodes in the same woman	FDA request Jul-2023
		Section 9.2.3, Additional Exclusion Criteria for Specific Analysis	Correction of period of ascertainment for syndromic or chromosomal anomalies in the infant (at birth and up to 12 months after birth)	Update
		Section 9.5, Study Size	Updated to consider the addition of other data sources if needed to achieve the study target size	FDA request Jul-2023
		Section 9.7.3, Comparative Safety Analysis	The dependent variable in the propensity score has been revised to be exposure status ascertained from 30 days before the LMP to the end of the first trimester (previously, it included the entire pregnancy)	FDA request Jul-2023
V4.0	17-Apr-2023	PASS Information	Updated PASS information	MAH transfer from Biohaven Pharmaceuticals to Pfizer Inc
		Section 6, Milestones and Timelines	Updated to reflect sequence of revised protocol submissions	Update
		Section 8, Research Question and Objectives; Section 9.3.2.2.1, Primary Fetal/Infant Study Outcomes	Added footnote to clarify that the primary objective is to evaluate the risk of MCMs in pregnant women with migraine exposed to rimegepant in the first trimester	FDA request Dec-2022
		Section 9.2.1.2, Ascertainment of Migraine	Added recent information on background prevalence of migraine	Update
		Section 9.2.2, Inclusion and Exclusion Criteria	Amendment to allow identification of ongoing and completed pregnancies	Amendment
		Section 9.2.5, Follow-up	Updated description of infant follow-up, aligned with the SAP	Align text with SAP

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Section 9.3.1, Exposure	Updated to reflect the eligibility criteria for subsequent pregnancies from the same woman Added cross-reference to the survey component to validate the proposed approach to determine the pre-pregnancy exposure window (median interval) for migraine medications	FDA request Dec-2022
		Section 9.3.1, Exposure; Section 9.7.1, Study Groups	The exposure window of 30-day before the estimated LMP was updated to reflect the exception for botulinum toxin for which the exposure window will include a 90-day period before the estimated LMP, based on the median interval between consecutive dispensings observed in the interim analyses	Update
		Section 9.3.2, Study Outcomes	Updated to clarify that the focus of validation is MCMs before final analyses and to clarify the contingency plan for earlier validation activities	FDA request Dec-2022
		Section 9.3.2, Study Outcomes	Updated available information on published studies of outcomes validation	Update
		Section 9.3.2.2.2, Secondary Fetal/Infant Study Outcomes	Updated to clarify that performance of algorithm for preterm birth ascertainment will be evaluated based on published data.	Update
		Section 9.3.3, Other Variables; Annex 3, Additional Information	Added number of pregnancies ending in spontaneous abortions to the baseline variables	Update
		Section 9.5, Study Size	Updated to clarify the plan to implement in case of failure to achieve the target size	FDA request Dec-2022
		Section 9.7.3, Comparative Safety Analysis	Updated to clarify that propensity score matching is the primary analysis method. Inverse probability of treatment weighting will be the first alternative method to explore if propensity score matching appears not to be feasible.	FDA request Dec-2022
		Section 9.7.7, Sensitivity Analyses	Added sensitivity analysis restricted to first observed pregnancy per woman in each study group	Update

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Section 10, Protection of Human Subjects; Section 11, Management and Reporting of Adverse Events/Adverse Reactions	Added language related to study components that require primary data collection (Survey Component) or review of unstructured data (Outcome validation via Adjudication)	Adoption of Pfizer non-interventional study protocol template
		Section 12, Plans for Disseminating and Communicating Study Results	Updated language	Adoption of Pfizer non-interventional study protocol template
		Annex 3, Additional Information	Updated information on teratogenic medications in Table 13	FDA request Feb-2023
		Annex 4	Included summary outline of the survey component on migraine medications use	Update
		All sections	Minor edits	Update
V3.0	08-Nov-2022	PASS Information	Updated PASS information	PRAC request Sep-2022
		Section 6, Milestones and Timelines	Updated to reflect study reporting to the EMA	PRAC request Sep-2022
		Section 7.1, Rimegepant and Other Treatments for Migraine	Updated to include current knowledge of rimegepant use in pregnancy and preclinical experience, and information on recommended treatments for migraine in Europe	PRAC request Sep-2022
		Section 7.5, Rationale	Updated to include reference to the EU risk management plan	PRAC request Sep-2022
		Section 8, Research Question and Objectives	Updated to formulate the research question	PRAC request Sep-2022
		Section 9, Study Design	Updated to clarify that MCMs are the primary outcome interest amongst all outcomes; to specify the measure of frequency and association for study outcomes	PRAC request Sep-2022
		Section 9.3.1, Exposure	Updated to clarify specific exposure window for study outcomes	PRAC request Sep-2022
		Section 9.3.2.2.1, Primary Fetal/Infant Study Outcomes	Amendment to add EUROCAT classification of MCMs	PRAC request Sep-2022

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Section 9.7.2, Descriptive Analyses	Added the strategy to evaluate the study's generalizability to pregnant women with migraine in the EU in interim reports; to include the EUROCAT total prevalence calculation for the final analyses	PRAC request Sep-2022
		Section 9.7.5, Statistical Analyses	Updated wording of definition of exposure ascertainment window for the preterm birth outcome; to update the measure of association and regression model to align with the SAP	Update
		Section 9.9, Limitations of the Research Methods	Amendment to include a discussion of the representativeness of the study population; inclusion of fetal losses in the estimation of the overall prevalence of MCMs; the potential for immortal time bias; the study size limitation for the analysis of specific types of MCMs	PRAC request Sep-2022
		All sections	Updated to align with the EMA PASS protocol template; updated section headings numbers	
		Section 9.3.2, Study Outcomes	Updated to describe the timeframe for validation of outcomes	FDA request Oct-2022
		Annex 3, Table 14; Section 9.3.3, Other Variables	Added anxiety disorder and obsessive-compulsive disorder to the list of variables	FDA request Oct-2022
		Annex 3, Table 13	Updated relevant exposure windows of specific medications	FDA request Oct-2022
V2.0	05-Aug-2022	Section 6, Milestones and Timelines	Updated to reflect protocol approval and the start of data collection	Update
		Section 9.2.2, Inclusion and Exclusion Criteria in Study Groups	Amendment, the ordering of inclusion/exclusion criteria has changed to reflect the eligible, ongoing pregnancies in each study group	FDA request Jul-2022
		Section 9.2.3, Inclusion and Exclusion Criteria in Study Groups	Updated the exclusion criteria for the analysis of MCMs	Update
		Section 9.3.1, Exposure; Section 9.7.2, Descriptive Analyses	Amendment to include a data-derived definition for the rimegepant potential indication. Include analyses of pregnancies exposed to acute only, preventive only, and acute and preventive migraine medications	FDA request Jul-2022

Amendment number	Date	Protocol section(s) changed	Summary of amendment(s)	Reason
		Section 9.3.2.3.2, Secondary Pregnancy Study Outcomes; Section 9.7.7, Sensitivity Analyses	Amendment to reference additional sensitivity analyses of the pre-eclampsia and/or eclampsia outcome	FDA request Jul-2022
		Section 9.3.2.2.1, Primary Fetal/Infant Study Outcomes; Section 9.7.5, Statistical Analyses; Section, 9.7.7 Sensitivity Analyses	Amendment to reference additional sensitivity analyses of the MCMs outcome	FDA request Jul-2022
		Section 9.3.2.2, Fetal/Infant Outcomes	Added a second algorithm for the MCM outcome in Table 6 and updated information on validation of outcomes	Amendment
		Section 9.3.3, Other Variables; Section 9.7.4, Missing Data; Section 9.9, Limitations of the Research Methods	Added the variable race and ethnicity	FDA request Jul-2022
		Section 9.3.3, Other Variables	Added other variables to align with SAP v0.3	Update
		Section 9.7.5, Statistical Analyses	Clarified the unit of analysis for the MCM outcome analysis	Amendment
		Section 9.7.7, Sensitivity Analyses	Added subgroup analyses for MCM by preterm birth status, and various sensitivity analyses identified during the first interim analysis	Amendment
		Annex 3, Additional Information	Aligned content of the tables with SAP v0.3	Update
		All sections	Minor edits	Update

EMA = European Medicines Agency; EU = European Union; EUROCAT = European Surveillance of Congenital Anomalies programme; FDA = Food and Drug Administration; MAH = marketing authorization holder; MCM = major congenital malformation; PASS = postauthorization safety study; PRAC = Pharmacovigilance Risk Assessment Committee; SAP = statistical analysis plan.

6. MILESTONES

The study milestones are summarized in Table 1.

Start of study observation period: The study start date is the date on which rimegepant is first available in the participating United States (US) data source. Rimegepant was approved by the US Food and Drug Administration (FDA) on 27-Feb-2020. The planned start of the study observation period is 16-Mar-2020, coinciding with the availability of rimegepant in the US.

End of study observation period: The end of the study observation period is the date on which the final data point has been collected from the data source following fulfillment of the target study size, expected in 2027 (see Figure 1). Annual interim study reports will be submitted to the FDA and the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee starting in 2022. The number of pregnancies exposed to rimegepant and the number of pregnancies in the unexposed comparator groups, selected characteristics of the pregnancies, and frequency of the study outcomes in each study group will be reported annually during the study observation period to inform the study size, estimate the predicted study power, inform the feasibility of obtaining the target study size, provide an estimate of when the target study size will be reached, and discuss the representativeness of the US-based study population for the European Union (EU) based population of pregnant women with migraine. The final study report will be submitted to the FDA and EMA within 1 year of the study completion, expected by April 2029, or earlier if the target study size is reached earlier (see Table 1).

Note: Upon approval of protocol V1.0 by the FDA, the study was registered in ClinicalTrials.gov and the European Union Electronic Register of Post-Authorisation Studies.

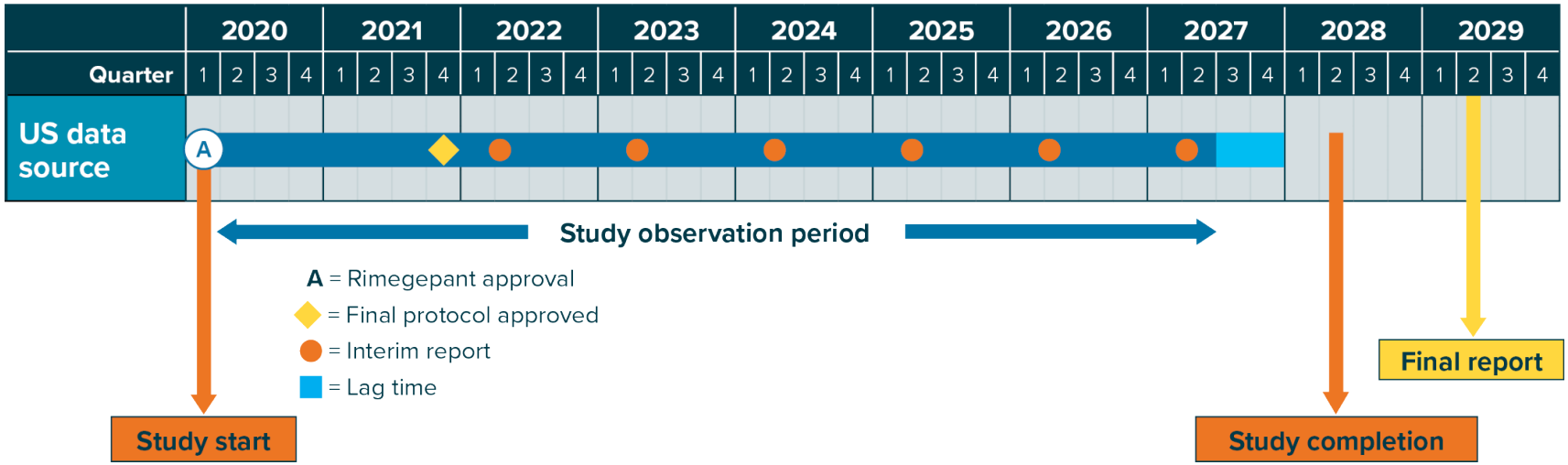
Table 1: Study Milestones

Milestone	Planned/actual date
Draft protocol submission to FDA	22-Sep-2020
Final protocol V1.0 approval from FDA	14-Dec-2021
Registration in the EU PAS Register	24-Feb-2022
Updated protocol V2.0 submission to FDA	12-Aug-2022
Updated protocol V3.0 submission to EMA	29-Nov-2022
Updated protocol V3.0 submission to FDA	13-Dec-2022
Updated protocol V4.0 submission to FDA and EMA	28-Apr-2023
Start of study observation period	16-Mar-2020
Start of data collection[a]	15-Dec-2021
End of study observation period	June 2027
End of data collection[b]	April 2028
Annual interim report to FDA	April 2022
Annual interim report to EMA	November 2022
Annual interim report to FDA and EMA	April 2023

Milestone	Planned/actual date
Annual interim report to FDA and EMA	April 2024
Annual interim report to FDA and EMA	April 2025
Annual interim report to FDA and EMA	April 2026
Annual interim report to FDA and EMA	April 2027
Final study report	Within 1 year of availability of the final analytical data set

EMA = European Medicines Agency; EU PAS Register = European Union Electronic Register of Post-Authorisation Studies; FDA = Food and Drug Administration.
Note: Approvals by data protection, data custodian, ethics, and scientific review bodies are complete. The timeline for the final comparative analyses may be advanced if interim reports indicate that the target study size (see Section 9.5) can be attained earlier; the timeline for submission of the final study report to the FDA and EMA will be modified accordingly.
a. The start of data collection for secondary data use is “the date from which data extraction starts.”
b. The date from which the final analytical data set is available (end of data collection).

Figure 1: Study Milestone Overview



US = United States.

7. RATIONALE AND BACKGROUND

7.1. Migraine

Migraine is a common and debilitating neurological disorder that affects approximately 15% of the adult population. It is characterized by moderate-to-severe episodic unilateral pulsating headaches that last for 4 to 72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity, and association with nausea and/or photophobia and phonophobia (IHS, 2018).

Migraine is the 7th-highest specific cause of disability worldwide (Petrovski et al., 2018; Stovner et al., 2007; Vos et al., 2012). Approximately 63% of individuals with migraine experience 1 to 4 migraines per month (Lipton et al., 2007). Migraine is more prevalent among women than among men, particularly during reproductive years (Croop et al., 2019). The prevalence of migraine among men and women in the US adult population was found to be 9.7% (95% confidence interval [CI], 9.1%-10.4%) and 20.7% (95% CI, 19.8%-21.6%), respectively (Burch et al., 2018). The prevalence of migraine in women of childbearing age was 20.6% in the age group 18-29 years, 28.4% in the age group 30-39 years, and 25.8% in the age group 40-49 years (Buse et al., 2013). Migraine frequency may decrease during pregnancy, particularly during the second and third trimesters, and increase again after delivery (Kvisvik et al., 2011). The cumulative prevalence of migraine during the whole pregnancy was approximately 20% in 4 studies, including more than 34,000 patients (Tanos et al., 2019). However, some studies noted that approximately 40% of patients with any migraine type experienced headache deterioration in early pregnancy (Frederick et al., 2014).

Chronic migraine is described by the International Headache Society (IHS) as a headache that occurs on 15 or more days per month for more than 3 months, which, on at least 8 days per month, has the features of migraine headache (IHS, 2018). The prevalence of chronic migraine has been estimated to range from 1.4% to 2.2% (Natoli et al., 2010).

7.2. Rimegepant and Other Treatments for Migraine

Nurtec® orally disintegrating tablet (rimegepant, previously known as BHV-3000), a calcitonin gene–related peptide (CGRP) receptor antagonist developed by Biohaven Pharmaceuticals, Inc. (Biohaven), was approved by the US FDA in February 2020 for the acute treatment of migraine with or without aura in adults. In May 2021, rimegepant was also approved by the US FDA for the preventive treatment of episodic migraine in adults. In April 2022, Vydura® (rimegepant) received marketing authorization in the EU for the acute treatment of migraine with or without aura in adults and for the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month. Calcitonin gene–related peptide is an endogenous 37–amino acid peptide contained within pain signaling nociceptive afferents that is thought to play a causal role in migraine (Edvinsson, 2004; Lassen et al., 2002). Multiple lines of clinical evidence point to a role for CGRP in migraine pathophysiology: (1) serum levels of CGRP are elevated during migraine (Goadsby et al., 1990), (2) treatment with antimigraine medication returns CGRP levels to normal coincident with pain relief (Goadsby and Edvinsson, 1993), and (3) intravenous CGRP infusion produces lasting pain in individuals without migraine and in those with migraine (Lassen et al., 2002; Petersen et al., 2005).

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 (Durham, 2004).

As of 03-Sep-2020, more than 7,200 patients have participated in rimegepant clinical studies. Among these patients, more than 3,800 patients with migraine have received a single dose of either 75-mg rimegepant or placebo in phase 2b/3 studies. In the pivotal prevention study, a total of 527 subjects received rimegepant (every other day or every other day plus as needed up to once daily) for at least 6 months, and 311 subjects received rimegepant for at least 1 year. Collectively, the current data demonstrate a favorable benefit-risk profile for rimegepant in the acute and preventive treatment of migraine (Nurtec ODT PI, 2021).

No adequate data are available on the developmental risk associated with rimegepant use 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 (e.g., decreased fetal body weight, increased incidence of fetal variations). These highest dose test exposures also resulted in maternal toxicity and were approximately 45 times the maximum recommended human dose (Nurtec ODT PI, 2021).

As of 31-May-2020, a total of 32 women treated with rimegepant had reported pregnancies during the rimegepant clinical development program (in addition to 1 pregnancy reported in a partner assigned to receive rimegepant). Of these 32 treated women, 11 reported live births (in addition to 1 partner pregnancy), 6 reported spontaneous abortions, 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. Four women assigned to receive placebo reported pregnancies (in addition to 1 pregnancy reported in a partner assigned to placebo): 1 resulted in a live birth (in addition to 1 partner pregnancy), 2 had subsequent negative urine pregnancy test results, and 1 had an unknown pregnancy outcome. The rimegepant clinical development program remains ongoing, and pregnancy data will continue to be collected and monitored. One case on drug exposure during pregnancy was collected during postmarketing pharmacovigilance; however, the outcome of the pregnancy is not available, and no adverse events (AEs) were reported.

Other pharmacological treatments for the acute treatment of migraine include NSAIDs, acetaminophen, triptans, ergots, and opioids. Triptans are commonly used in individuals with migraine who have no relief of symptoms with NSAIDs or acetaminophen (Lew and Punnapuzha, 2020). Triptans specifically bind 5-HT1B/D receptors, having vasoconstrictive effects due to their mechanism of action on serotonin (5-HT) 1B receptors on the smooth muscle cells of blood vessels, and they therefore are contraindicated in patients with cardiovascular risks (Lew and Punnapuzha, 2020). To date, 7 triptans have been approved by the US FDA for acute treatment of migraine: sumatriptan, eletriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, and almotriptan (Lew and Punnapuzha, 2020). Ergots, such as ergotamine and dihydroergotamine, have been mostly replaced by triptans. Opioids are occasionally used to treat migraine (Gazerani and Cairns, 2020).

Other preventive treatments for migraine in the US include tricyclic antidepressants (amitriptyline and nortriptyline), selective serotonin reuptake inhibitors (citalopram, sertraline, fluoxetine, and paroxetine), serotonin-norepinephrine reuptake inhibitor (venlafaxine), beta-blockers (propranolol, metoprolol, nadolol, and atenolol), anti-epileptic medications (gabapentin, topiramate, and divalproex) (Hoffman et al., 2019), and botulinum toxin. Calcitonin gene–related peptide therapy monoclonal antibodies that have recently been approved for the prophylaxis of migraine include erenumab, fremanezumab, galcanezumab (Ha and Gonzalez, 2019), and eptinezumab. Persistence with migraine preventive therapy seems to be low, and switching medications or re-start after treatment discontinuation is common (Hepp et al., 2017; Woolley et al., 2017). Many patients also use acute treatments while on preventive treatment (Woolley et al., 2017).

In Europe, the recommended treatments for acute migraine episodes include nonsteroidal NSAIDs and paracetamol as a first-line treatment. Paracetamol is specially indicated as first-line treatment in pregnant women. Second-line treatments include the triptans (Eigenbrodt et al., 2021). Third-line treatments include ditans (lasmiditan) and CGRP (ubrogepant and rimegepant). For chronic migraine, first-line preventive treatments include beta-blockers without intrinsic sympathomimetic activity (atenolol, bisoprolol, metoprolol, or propranolol), topiramate, and candesartan; second-line preventive treatments include flunarizine, sodium valproate, and amitriptyline; and third-line treatments include CGRP monoclonal antibodies (erenumab, fremanezumab, galcanezumab, and eptinezumab) (Eigenbrodt et al., 2021; Sacco et al., 2022).

Information on rimegepant and other common treatments for migraine in the US and Europe is summarized in Table 2.

Table 2: Information About the Use of Rimegepant in the United States and Europe

Topic	United States	Europe
Common physician specialties that diagnose migraine	Neurology	Neurologist
Common prescriber types for migraine (e.g., specific specialists or GPs)	Neurologists, GPs, psychiatrists	GPs, specialists
List of other common treatments for migraine	• Acetaminophen, NSAIDs, triptans (sumatriptan, eletriptan, naratriptan, zolmitriptan, rizatriptan, frovatriptan, and almotriptan), ditans (lasmiditan), ergots (ergotamine and dihydroergotamine), and opioids[a] • CGRP receptor antagonists (ubrogepant[a], atogepant[b], rimegepant[a, b], and zavegepant[a]) • CGRP monoclonal antibodies (erenumab, fremanezumab, eptinezumab, and galcanezumab)[b] • Beta-blockers (propranolol, timolol, bisoprolol, metoprolol, atenolol, and nadolol)[b]	For acute treatment: • First-line medication: NSAIDs (acetylsalicylic acid, ibuprofen or diclofenac potassium) • Second-line medication: Triptans; when triptans provide insufficient pain relief, combine with fast-acting NSAIDs • Third-line medication: ditans, gepants For preventive treatment: • First-line medication: – Beta-blockers (propranolol, metoprolol, atenolol, bisoprolol) – Topiramate – Candesartan

Topic	United States	Europe
	• Anti-epileptics (gabapentin, topiramate, valproate, divalproex)[b] • Antidepressants (amitriptyline, fluoxetine, venlafaxine)[b] • Botulinum toxin (onabotulinumtoxinA)[b]	• Second-line medication: – Flunarizine – Amitriptyline – Sodium valproate[d] • Third-line medication – CGRP monoclonal antibodies
Position of rimegepant among all treatments for acute treatment of migraine	First-line treatment[c]	Third-line treatment
Approved indications and dosages for rimegepant	Rimegepant is approved for the acute treatment of migraine with or without aura in adults. The recommended dose is 75 mg taken orally, as needed. Rimegepant is also approved for the preventive treatment of episodic migraine in adults. The recommended dose is 75 mg taken orally every other day. The maximum dose in a 24-hour period is 75 mg.	Rimegepant is approved for the acute treatment of migraine with or without aura in adults. The recommended dose is 75 mg rimegepant, as needed, once daily. Rimegepant is also approved for the preventive treatment of episodic migraine in adults who have at least 4 migraine attacks per month. The recommended dose is 75 mg rimegepant every other day. The maximum dose per day is 75 mg.

CGRP = calcitonin gene–related peptide; GP = general practitioner; NSAIDs = nonsteroidal anti-inflammatory drugs.
a. Acute treatment of migraine.
b. Preventive treatment of migraine.
c. Approved as first-line treatment. It is included in some formularies as second-line treatment.
d. Contraindicated in women of childbearing potential.

7.3. Migraine and Pregnancy Outcomes

Pregnant women experiencing migraine appear to be at higher risk than pregnant women without migraine for some complications, including gestational hypertension, pre-eclampsia, small-for-gestational-age (SGA) birth, low birth weight, preterm birth, and spontaneous abortion (Tanos et al., 2019).

The risk of pre-eclampsia during pregnancy was higher in women with migraine than in women without migraine in a meta-analysis, including 9 studies and approximately 74,000 women (adjusted pooled odds ratio [OR], 1.94; 95% CI, 1.37-2.76) (Aukes et al., 2019).

The evidence for the risk of SGA births among pregnant women with migraine is not clear. In 1 cohort study, the percentage of SGA births was only slightly higher for women with migraine (17.7%) than for women without migraine (16.8%) (Chen et al., 2010), although these results were not confirmed in a prospective study of 376 pregnant women with migraine or tension headache and 326 pregnant women without headache (Marozio et al., 2012). In a meta-analysis of 2 studies, the adjusted pooled OR for SGA births was 1.06 (95% CI, 0.99-1.14) (Aukes et al., 2019). In a literature review of observational studies, the incidence of low birth weight in infants born to women with

migraine (range: 6.8%-18.7%) was higher compared with pregnant women without migraine (range: 3.6%-8%) (Tanos et al., 2019). Results from a meta-analysis, including 3 studies and more than 68,000 pregnant women, suggested an increased risk of low birth weight in women with migraine compared with women without migraine (adjusted pooled OR, 1.27; 95% CI, 0.89-1.82) (Aukes et al., 2019).

Five studies have reported the risk of preterm birth in pregnant women with migraine. The prevalence of preterm birth was higher in pregnant women with migraine (range: 7.1%-28%) versus nonmigraine (range: 2.8%-11.4%) (Tanos et al., 2019). Results from a meta-analysis, including 2 studies published between 2008 and 2010, suggested an increased risk of preterm birth in pregnant women with migraine compared with that among pregnant women without migraine (adjusted pooled OR, 1.25; 95% CI, 1.13-1.38) (Aukes et al., 2019).

The risk of spontaneous abortion in pregnant women was investigated in a recent study conducted in the Danish National Registries (Skajaa et al., 2019). The prevalence of spontaneous abortion was 11.3% among pregnant women with migraine and 10.3% among pregnant women without migraine, resulting in a prevalence ratio of 1.10 (95% CI, 1.05-1.15).

7.4. Exposure to Other Treatments for Migraine and Pregnancy Outcomes

The safety profiles of acute treatments for migraine other than rimegepant during pregnancy are diverse. Acetaminophen is usually recommended as the first option for pregnant and breastfeeding women due to its safety profile (Amundsen et al., 2019), although some studies reported an increased risk of pre-eclampsia and thromboembolic diseases with acetaminophen exposure during pregnancy (Rebordosa et al., 2010). In a recent study, the exposure to NSAIDs during the first trimester of pregnancy was associated with increased risk of SGA births among women with autoimmune conditions (Delker et al., 2023). Ergotamine and dihydroergotamine have been associated with adverse pregnancy outcomes, such as low birth weight or preterm birth (Bánhidy et al., 2007; Bérard and Kori, 2012).

The evidence regarding the safety of triptans is scarce, although they have been used since the early 2000s (Duong et al., 2010). Most of the evidence comes from pregnancy registries, although more recently, some studies have been conducted in electronic health care databases. In this study, the authors compared the results from a completed, 16-year, international, prospective pregnancy registry (the sumatriptan, naratriptan, and sumatriptan/naproxen pregnancy registry between January 1996 and September 2012) (Ephross and Sinclair, 2014) with a retrospective analysis conducted in the Truven Health MarketScan® Commercial Claims and Encounters and Medicare Supplemental and Coordination of Benefits Databases for the period of 1996 to 2012 (Yusuf et al., 2018). In both studies, the majority of pregnant women were treated with triptans during the first trimester of pregnancy. The risk of major birth defects for sumatriptan exposure during the first trimester was 4% in both the claims analysis and pregnancy registry. For naratriptan and sumatriptan/naproxen sodium, the risk of major birth defects for exposure during the first trimester was 0% and 3.6% in the claims analysis and 2.2% and 0% in the registry, respectively. The risk of spontaneous abortions in women exposed to sumatriptan, naratriptan, and sumatriptan/naproxen sodium during the first trimester was 18%, 17.4%, and 18.9% in the claims analysis and 6.6%, 9.6%, and 20% in the registry, respectively. Finally, the risk of major birth defects in women exposed to sumatriptan, naratriptan, and sumatriptan/naproxen sodium during the second and third trimesters was 3.9%,

14.3%, and 7.1% in the claims analysis and 3.1%, 0%, and 0% in the registry, respectively. In a meta-analysis comparing risk of some pregnancy outcomes between pregnant women with migraine treated with triptans versus women with migraine not treated with triptans, the authors did not find an increased risk of congenital malformations (pooled OR, 0.84; 95% CI, 0.61-1.16), spontaneous abortions (pooled OR, 1.27; 95% CI, 0.58-2.79), or preterm birth (pooled OR, 0.90; 95% CI, 0.35-2.30); when compared with healthy women, there were no increased rates of major congenital malformations (MCMs) (OR, 1.18; 95% CI, 0.97-1.44) or premature births (OR, 1.16; 95% CI, 0.67-1.99); however, there was a significant increase in the rates of spontaneous abortions (OR, 3.54; 95% CI, 2.24-5.59). When the migraine no-triptan group was compared with healthy controls, a significant increase in the rates of MCMs was found (OR, 1.41; 95% CI, 1.11-1.80) (Marchenko et al., 2015). A recent prospective observational cohort study conducted in Germany reported no increased risk of pregnancy outcomes or birth defects in pregnant women exposed to triptans compared with pregnant women with migraine untreated or pregnant women without migraine (Spielmann et al., 2018). There was no evidence of an increased risk of major malformations, low birth weight, or prematurity associated with triptans in another systematic review and meta-analysis of medications used for the treatment of migraine (Dudman et al., 2022).

A Danish population-based study found an increased risk of pregnancy-associated hypertension, spontaneous abortion, and preterm birth and no increased risk of birth defects and SGA births associated with migraine. Among women who took migraine treatment (either acute, preventive, or both) compared with pregnant women who were not treated for migraine, no increased risk of spontaneous abortion, pregnancy-associated hypertension, adverse birth outcomes including congenital malformations, or adverse neonatal or neurological outcomes in offspring was found (Skajaa et al., 2019). Medications used to prevent or treat attacks of primary headache (migraine, tension headache, cluster headache, and other trigeminal autonomic cephalalgias) in women who were pregnant (or who were attempting to become pregnant), postpartum, or breastfeeding have been evaluated in a systematic literature review. The authors found that preventive migraine treatments, including anti-epileptics (except lamotrigine), venlafaxine, tricyclic antidepressants, benzodiazepines, beta-blockers, prednisolone, and oral magnesium, may be associated with increased risk of fetal/infant adverse effects, but calcium channel blockers and antihistamines may have a low risk of adverse effects (Saldanha et al., 2020). Among anti-epileptics, valproic acid is teratogenic and contraindicated in pregnancy, and topiramate has been associated with oral clefts at birth (Bromfield et al., 2008; Hernandez-Diaz et al., 2018; Tomson et al., 2018).

7.5. Rationale

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

plan for Vydura®, included as a Category 3 postauthorization safety study, which aims to provide information to address the safety concern of "missing information" on the use of rimegepant in pregnant women.

8. RESEARCH QUESTION AND OBJECTIVES

The primary research question of this study is: Is there an increased risk of adverse fetal, maternal, and infant outcomes in women with migraine exposed to rimegepant during pregnancy?

The primary objective is to evaluate the risk of pregnancy and infant outcomes with MCMs as the primary outcome of interest and other primary outcomes including spontaneous abortions, fetal deaths/stillbirths, and SGA births among women with migraine exposed to rimegepant during pregnancy,[2] and in 2 rimegepant-unexposed comparator groups. Specific objectives are as follows:

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

9. RESEARCH METHODS

9.1. Study Design

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

The study will include the following study groups:

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

[2] See Table 10 for the relevant exposure window for each study outcome. The primary analysis will assess the association between first trimester rimegepant exposure and risk of MCMs.

The primary outcome of interest is:

- MCMs

Other primary outcomes are as follows:

- Pregnancy outcomes (spontaneous abortions, fetal deaths/stillbirths)
- Fetal/infant outcomes (SGA births)

The secondary outcomes are as follows:

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

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

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

The study groups of pregnant women with migraine who are treated with rimegepant, pregnant women with migraine treated with medications indicated for migraine other than rimegepant, and pregnant women without migraine unexposed to rimegepant will be identified using data from medical and pharmacy claims. Treatments other than rimegepant that are indicated for the treatment of migraine include NSAIDs, acetaminophen, triptans, ergots, opioids, beta-blockers, anti-epileptics, antidepressants, and botulinum toxin (see Annex 3, Table 12).

Claims data will be used as the main source of data for ascertaining the exposure, study outcomes, and covariates. Patterns of use of rimegepant and other medications indicated for the treatment of migraine will be described in a pre-pregnancy period of 6 months. The data obtained on the use of these medications will be used to determine the appropriate time window for ascertainment of pregnancy exposure to these medications (see Section 9.3.1). Characteristics of pregnant women will be described at baseline using data from the relevant time period (depending on the variable) before the start of pregnancy (estimated first day of the last menstrual period [LMP]) and during pregnancy (see Section 9.3.3). Women will be followed from the start through the end of pregnancy plus a 42-day postpartum period to determine the prevalence of pregnancy outcomes, including spontaneous abortions, fetal deaths/stillbirths, elective terminations, and pre-eclampsia/eclampsia. The follow-up period will vary according to the outcome evaluated. Infants born to pregnant women in each study group will be followed through 1 year after birth to determine the prevalence of MCMs, SGA births, and preterm births.

The prevalence, as a measure of frequency, of all study outcomes will be calculated in the 3 study groups, and RR, as a measure of association, will be estimated between the rimegepant-exposed

pregnancies and pregnancies in the primary comparator group, as well as between rimegepant-exposed pregnancies and pregnancies in the secondary comparator group (see Section 9.7.5).

9.2. Setting

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

9.2.1. Population

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

- Has a pregnancy code or a recorded pregnancy outcome (i.e., live birth, stillbirth, spontaneous abortion, or elective termination) within the study observation period
- Be aged 16 to 49 years, inclusive, at the estimated LMP within the study observation period.

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

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

9.2.1.1. Identification of Pregnancies

Potential pregnancies will be identified from women who have at least 1 medical claim with a pregnancy-related *International Classification of Diseases, 10th Revision* (ICD-10) diagnosis or procedure code, Current Procedural Terminology (CPT) code, or Healthcare Common Procedure Coding System (HCPCS) code. Diagnosis codes include those related to pregnancy, childbirth, and the puerperium (O00-O9A); weeks of gestation (Z3A); outcome of delivery (Z37); encounters for antenatal screening of the mother (Z36); supervision of normal/high risk pregnancy (Z34/O09); and maternal postpartum care (Z39). Codes for pregnancy-related procedures include those performed on the products of conception (3E0E, 4A0H, 4A0J, 4A1H, 4A1J). A pregnancy episode is defined as the duration of time from the estimated LMP (pregnancy start date) through the pregnancy outcome date (pregnancy end date) (Bertoia et al., 2022; Matcho et al., 2018).

The algorithm to identify pregnancy episodes uses all available codes indicating weeks of gestation (Z3A.00 to Z3A.42, excluding Z3A.49). The nonspecific Z3A codes (Z3A.00, weeks of gestation of pregnancy not specified and Z3A.01, < 8 weeks gestation of pregnancy) are included to identify pregnancy episodes that have only 1 or both codes, as these codes may be the only ones present for pregnancies ending in a loss or termination. The code Z3A.49 (> 42 weeks gestation of pregnancy) is excluded because only a very small number of women have this code, and it is not associated with a specific gestational period. For each woman, and for each observed Z3A code (starting with the earliest claim date), the algorithm subtracts the weeks of gestation indicated by the Z3A code from the date of service indicated in the claim to estimate LMP. These LMP estimations are repeated for each available Z3A code until the last claim date associated with a Z3A code is reached, resulting in multiple estimated LMPs for each woman. Because Z3A.00 codes were observed at various weeks

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

Several data cleaning steps are incorporated into the algorithm, for example, to remove duplicate claim lines and sequentially sort each woman's estimated LMP. Then, to identify and separate pregnancy episodes, the algorithm creates LMP clusters by grouping together all estimated LMPs within 6 weeks of one another (starting with the earliest estimated LMP and going forward to set up a 6-week window). The 6-week window was chosen based on the minimum number of weeks required between pregnancies derived from previous publications (Hornbrook et al., 2007; Matcho et al., 2018). The final data cleaning steps remove the nonspecific Z3A codes (and associated LMP estimates) if specific Z3A codes are present within a cluster. In the last step of the algorithm, LMP for each pregnancy episode is estimated by using the median date within each LMP cluster.

A small fraction of pregnancies do not have Z3A codes; in these cases, Optum uses an outcomes-based algorithm that estimates LMP by counting back the number of weeks from the occurrence of a pregnancy outcome, with varying lengths of gestation assigned for different pregnancy outcomes (Hornbrook et al., 2007).

To ensure repeated pregnancy outcome codes that pertain to the same pregnancy are not counted as separate pregnancies, the algorithm requires a minimum number of weeks to have passed between any pair of consecutive pregnancy outcomes in the same woman. This interval depends on the pregnancy outcomes. For example, the minimum interval allowed between a live birth and a subsequent live birth is 24 weeks, while it is 10 weeks between a live birth and a spontaneous abortion (Bertoia et al., 2022). Subsequent pregnancy outcome codes that occur inside the minimum period between pregnancies are considered to be from the preceding pregnancy episode.

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

9.2.1.2. Ascertainment of Migraine

Many strategies have been used to identify migraine from electronic health data, with prevalence in pregnant women or in the general population ranging from 1% to 30% (see Table 3). Of note, some studies intended to identify patients with migraine and others intended to identify subsets of patients with migraine, such as those treated with preventive medications. One study validated an algorithm with good results (sensitivity, 78%; specificity, 73%), but the target population was patients with undiagnosed chronic migraine among patients with a claim for migraine but no claims for chronic migraine (Pavlovic et al., 2019).

Recent reports from the FDA that quantified migraine/headache as a baseline variable reported a prevalence of 2.5% ascertained from 90 days before pregnancy through the end of the first trimester in pregnant women with a linked child in years 2000 to 2019 in Sentinel (Suarez et al., 2022); use of triptans was 1.2% in the 90 days before pregnancy and 0.8% in the first trimester. Also using linked pregnancies from Sentinel, the prevalence of migraine/headache was 5.2%, with ascertainment from

90 days before pregnancy through the end of the first trimester among pregnant women unexposed to topiramate in years 2000 to 2015 (Lyons et al., 2022).

One reason the ascertainment of migraine is challenging is that the diagnosis seems to be under-recorded in claims data. One study identified persons with migraine using a questionnaire with 85% sensitivity and 97% specificity and then explored their claims patterns in a US health care system (Kolodner et al., 2004). Of the questionnaire-identified subjects with migraine, 60% did not have claims for migraine or headache in the 24 months before the interview and approximately 25% had not filed a claim for medications commonly used to treat migraine (Kolodner et al., 2004).

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

Author (year)	Algorithm	Comments
Chen et al. (2010)	Using Taiwanese national data sets, the authors identified pregnant women with migraine as follows: "Of these women, 16 042 had visited ambulatory care centers for treatment of migraines (ICD-9-CM code 346) within 2 years before index delivery. We selected only patients who had at least 3 consensus migraine diagnoses … Ultimately, 4,911 women with migraines were included in the study cohort."	Prevalence was about 1% among pregnant women who had a singleton. Not validated.
Hepp et al. (2017)	To identify patients with chronic migraine in MarketScan, the authors required at least 1 claim with a 346.7 ICD-9-CM code (chronic migraine) and at least 1 prescription for preventive treatment. Excluded were patients who started an antidepressant and had a claim for depression in the previous year; same for epilepsy/anti-epileptic drugs and heart failure/beta-blockers.	Prevalence of chronic migraine was 0.06%. Not validated.
Woolley et al. (2017)	Using MarketScan, the authors identified persons with migraine who were receiving preventive treatment as those with dispensings for a migraine preventive medication (topiramate, beta-blocker, or tricyclic antidepressant) and a migraine diagnosis (ICD-9-CM 346.xx) in the 12 months before the first prescription.	Prevalence of migraine cannot be assessed from the results. Not validated.
Yusuf et al. (2018)	Using MarketScan, the authors identified women with migraine as those who met at least 1 of the following criteria: "One medical claim with a migraine diagnosis (ICD-9 346.xx, in any position) associated with an inpatient stay; or "One medical claim with a migraine diagnosis (ICD-9 346.xx, in any position) associated with a neurologist visit; or "Two medical claims with a migraine diagnosis (ICD-9 346.xx, in any position) associated with an outpatient physician or ED visit 7-180 days apart; or "One medical claim with a migraine diagnosis (ICD-9 346.xx, in any position) associated with an outpatient physician visit or ED visit AND 1 claim for a dispensing/administration of a migraine-specific acute treatment 7-180 days apart; or "Two claims for a dispensing/administration of a migraine-specific acute treatment 7-180 days apart"	Prevalence of migraine cannot be ascertained; the authors report 1,750,000 women 10-55 years old with migraine in MarketScan. This algorithm is similar to the one by Hoffman et al. (2019), described in the next row. Not validated.

Author (year)	Algorithm	Comments
Hoffman et al. (2019)	Criteria applied hierarchically in Optum data: 1a. One or more inpatient claims for migraine and 1 or more outpatient or ED claim for migraine, 7-180 days apart 1b. One or more inpatient claims for migraine and 1 or more dispensings for acute migraine-specific treatments, 7-180 days apart (1a and 1b identified 1,500 patients) 2. Two or more outpatient or ED claims for migraine, 7-180 days apart (22,500 patients) 3. One or more outpatient or ED claims for migraine and 1 or more dispensings for acute migraine-specific treatments, 7-180 days apart (15,300 patients) 4. Two or more dispensings for acute migraine-specific treatments, 7-180 days apart (50,000 patients) 5. One or more claim for migraine and a visit to a neurologist (30,000 patients) In addition, epilepsy diagnoses during baseline resulted in exclusion	This algorithm identified one-third of the general population as having migraine. Acute migraine-specific treatments were triptans and ergotamines. Not validated.
Pavlovic et al. (2019)	Researchers used a structured interview to diagnose chronic migraine among patients with a diagnosis claim for migraine but without a diagnosis claim for chronic migraine from a large medical group in California. Per the selected algorithm, patients were identified as having undiagnosed chronic migraine if their probability of having chronic migraine was 0.55 or larger based on coefficients from a logistic regression model and their individual-level values for 4 variables measured in a 12-month period: having 15 or more claims for acute migraine medications, having 24 or more health care visits, being a female, and having claims for 2 or more preventive medication classes.	Prevalence of migraine cannot be ascertained. This algorithm was validated: sensitivity was 78% and specificity was 73%.
Skajaa et al. (2019)	Using the Danish nationwide registries, the authors identified pregnancies in women with migraine as "pregnancies among women with a diagnosis of migraine during a hospital encounter (inpatient, outpatient, or emergency) between 01-Jan-1995 and the date of pregnancy end, or with at least 2 outpatient dispensings of a migraine-specific acute or preventive medication between 01-Jan-2004 and the date of pregnancy end." The authors' comment: "Medication proxies were used to identify migraine diagnoses not resulting in a hospital contact, because diagnoses in the primary health care sector are not captured in Danish registries."	This resulted in a prevalence of about 9.5% among pregnant women. Not validated.

Author (year)	Algorithm	Comments
Wood et al. (2021)	Using MarketScan, the authors identified women with migraine among pregnant women as women who met at least 1 of the following criteria: Primary definition: Two or more 346.xx ICD-9-CM codes in the 90 days before LMP One or more 346.xx ICD-9-CM codes in the 90 days before LMP and a prescription for migraine One or more 346.xx ICD-9-CM codes in the 90 days before LMP and a neurology encounter Two or more 346.xx ICD-9-CM codes at any time during the study period and a neurology encounter Secondary definition: 1 or more 346.xx ICD-9-CM codes in the 90 days before LMP	ICD codes were mostly sought for in the 90 days before LMP. The primary definition of migraine resulted in a prevalence of about 1%. The secondary definition (expected to be very sensitive) resulted in a prevalence of 1.3%. Not validated.

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

For this study, we propose to identify migraine as described in Table 4. This algorithm is a variation of those by Hoffman et al. (2019) and Yusuf et al. (2018) that incorporates *International Classification of Diseases, 10th Revision, Clinical Modification* (ICD-10-CM) codes and new migraine-specific medications, relaxes the time interval for subsequent codes in light of the findings by Kolodner et al. (2004), and removes a nonspecific criterion that resulted in a very large prevalence. This algorithm is generally aligned with the algorithm proposed by Wood et al. (2021) but with a broader interval for code identification and without the nonspecific criterion related to a visit to the neurologist.

Table 4: Identification of Patients With Migraine in this Study

Item	Description
Algorithm elements	
Migraine codes	ICD-10-CM: G43.xx (any code nested in G43) In the primary or another position
Migraine-specific treatments	Triptans, ergotamines, gepants, ditans, CGRP monoclonal antibodies (note: use of some of these treatments in a specified period determines exclusion from this study [see Section 9.2.2).
Period to identify migraine codes and migraine-specific treatments	Any time since January 2016 before the estimated LMP and through the end of pregnancy or end of the study observation period, whichever is first (note: this requires that pregnancies have been identified before migraine is ascertained). The minimum period of enrollment with medical and pharmacy benefits before pregnancy is specified in Section 9.2.1.
Algorithm criteria	
Patients meeting 1 or more of the following criteria will be considered as having migraine: 1. One or more inpatient claim for migraine and 1 or more outpatient/ED claim for migraine at least 7 days apart within 1 year 2. One or more inpatient claim for migraine and 1 or more dispensing for a migraine-specific treatment at least 7 days apart within 1 year 3. Two or more outpatient/ED claims for migraine at least 7 days apart 4. One or more outpatient/ED claim for migraine and 1 or more dispensing for a migraine-specific medication at least 7 days apart 5. Two or more dispensings for migraine-specific treatments at least 7 days apart	

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

9.2.2. Inclusion and Exclusion Criteria

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

A pregnancy that fulfills 1 or more of the following criteria will be excluded from the study:

- Has insufficient information to estimate LMP (e.g., if a completed pregnancy has no encoded pregnancy outcome and LMP was > 12 months before the last observed date in the extracted data, or if the woman disenrolled from the health plan during pregnancy)
- Has at least 1 pharmacy dispensing for ditans (i.e., lasmiditan) within a 5–half-life time window before the estimated LMP through whichever is first: end of pregnancy or end of the study period[3]
- Has at least 1 pharmacy dispensing for a CGRP receptor antagonist other than rimegepant (i.e., ubrogepant, atogepant, and zavegepant) within a 5–half-life time window before the estimated LMP through whichever is first: end of pregnancy or end of the study period[3]
- Has at least 1 pharmacy dispensing for CGRP monoclonal antibodies (i.e., erenumab, fremanezumab, eptinezumab, and galcanezumab) within a 5–half-life time window before the estimated LMP through whichever is first: end of pregnancy or end of the study period[3]

[3] Note that pregnancies without a recorded pregnancy outcome are excluded in a subsequent exclusion criterion.

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

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

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

Anti-emetic medications and calcium channel blockers will not be included among the medications that determine entry into the primary comparator group. Anti-emetic medications are more likely used in pregnancy for morning sickness than for migraine, and calcium channel blockers are not recommended for the treatment of migraine by existing guidelines. Regarding anti-emetic medications, 2 have been noted to be used for migraine in pregnancy: ondansetron and metoclopramide (Saldanha et al., 2020). Ondansetron is not approved for migraine in the US (Zofran PI, 2016), but it is widely used in pregnancy as an anti-emetic: 13% of women used it in the first trimester in 2013-2014 to treat morning sickness in a study in the US, and the prevalence of use appears to be increasing (Parker et al., 2018). Arguably, ondansetron might be more commonly used in pregnancy for morning sickness than for migraine. Metoclopramide is approved for gastroesophageal reflux and gastroparesis in the US (Reglan PI, 2017). Patterns of use in pregnancy in the US, peaking in the first trimester, which are relatively high in the second trimester and lower in the third trimester and before pregnancy, suggest that most of its use is related to nausea and vomiting in pregnancy (Taylor et al., 2017). Calcium channel blockers have been listed as drugs that can be used for the treatment of migraine in pregnancy (Saldanha et al., 2020); however, the American Academy of Neurology (Silberstein et al., 2012) and, more recently, the American Association of Family Physicians (Ha and Gonzalez, 2019) did not find evidence to support the use of drugs in this class for migraine prevention in adults.

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

9.2.2.1. Rimegepant-Exposed Group

The rimegepant-exposed group will include pregnancies in women with migraine treated with rimegepant who are eligible for the study and fulfill the following criteria:

- Have a migraine diagnosis that meets the criteria in Table 4 any time before the estimated LMP and through whichever is first: end of pregnancy or end of the study period[4]
- Have at least 1 pharmacy dispensing for rimegepant within the 30-day time window before the estimated LMP (see Section 9.3.1) and through whichever is first: end of pregnancy or end of the study period[4]
- Have a recorded outcome of pregnancy within the study period
- Had continuous enrollment in a health care plan with medical and pharmacy benefits during the 6-month period before the estimated LMP through a postpartum period of 42 days

9.2.2.2. Primary Comparator Group

The primary comparator group will include pregnancies in women with migraine exposed to medications for the treatment of migraine other than rimegepant. Each pregnant woman will need to fulfill all study eligibility criteria in addition to the following inclusion and exclusion criteria:

- Inclusion criteria:
  - Have a migraine diagnosis that meets the criteria in Table 4 any time before the estimated LMP and through whichever is first: end of pregnancy or end of the study period[4]
  - Have at least 1 pharmacy dispensing for a medication indicated for the treatment of migraine within the 30-day time window before the estimated LMP (see Section 9.3.1) and ending with whichever is first: end of pregnancy or end of the study period.[4] Medications indicated for the treatment of migraine include NSAIDs, acetaminophen, triptans, ergots, opioids, beta-blockers, anti-epileptics, antidepressants, and botulinum toxin (see Annex 3, Table 12)
  - Have a recorded outcome of pregnancy within the study period
  - Had continuous enrollment in a health care plan with medical and pharmacy benefits during the 6-month period before the estimated LMP through a postpartum period of 42 days
- Exclusion criterion:
  - Have at least 1 pharmacy dispensing for rimegepant within the 30-day time window before the estimated LMP and through whichever is first: end of pregnancy or end of the study period[4]

[4] Note that pregnancies without a recorded pregnancy outcome are excluded in a subsequent exclusion criterion.

9.2.2.3. Secondary Comparator Group

The secondary comparator group will include rimegepant-unexposed pregnancies in women without migraine. Each pregnant woman will need to fulfill all study eligibility criteria in addition to the following inclusion and exclusion criteria:

- Inclusion criteria:
  - Have no migraine diagnosis that meets the criteria in Table 4 any time before the estimated LMP through whichever is first: end of pregnancy or end of the study period[5]
  - Have a recorded outcome of pregnancy within the study period
  - Had continuous enrollment in a health care plan with medical and pharmacy benefits during the 6-month period before the estimated LMP through a postpartum period of 42 days
- Exclusion criterion:
  - Have at least 1 pharmacy dispensing for rimegepant within the 30-day time window before the estimated LMP through whichever is first: end of pregnancy or end of the study period[5]

9.2.3. Additional Exclusion Criteria for Specific Analysis

For the analysis of MCM, additional exclusion criteria for the rimegepant-exposed and comparator groups will be applied (see Section 9.3.2.2.1):

- Pregnancies and linked infants exposed to medications of known teratogenic risk within a 5–half-life time window before the estimated LMP or during pregnancy (see Annex 3, Table 13)
- Pregnancies and linked infants who experience infections known to cause congenital anomalies during pregnancy, TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, herpes simplex, and Zika virus disease)
- Pregnancies whose linked infants have syndromic or chromosomal anomalies (i.e., Down syndrome; trisomies 18 and 13, and other trisomies; monosomies and deletions from the autosomes; balanced re-arrangements and structural markers; Turner's syndrome, other sex chromosome abnormalities, and other chromosomal abnormalities) identified during pregnancy or at birth and up to 12 months after the infant's birth

9.2.4. Study Period

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

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

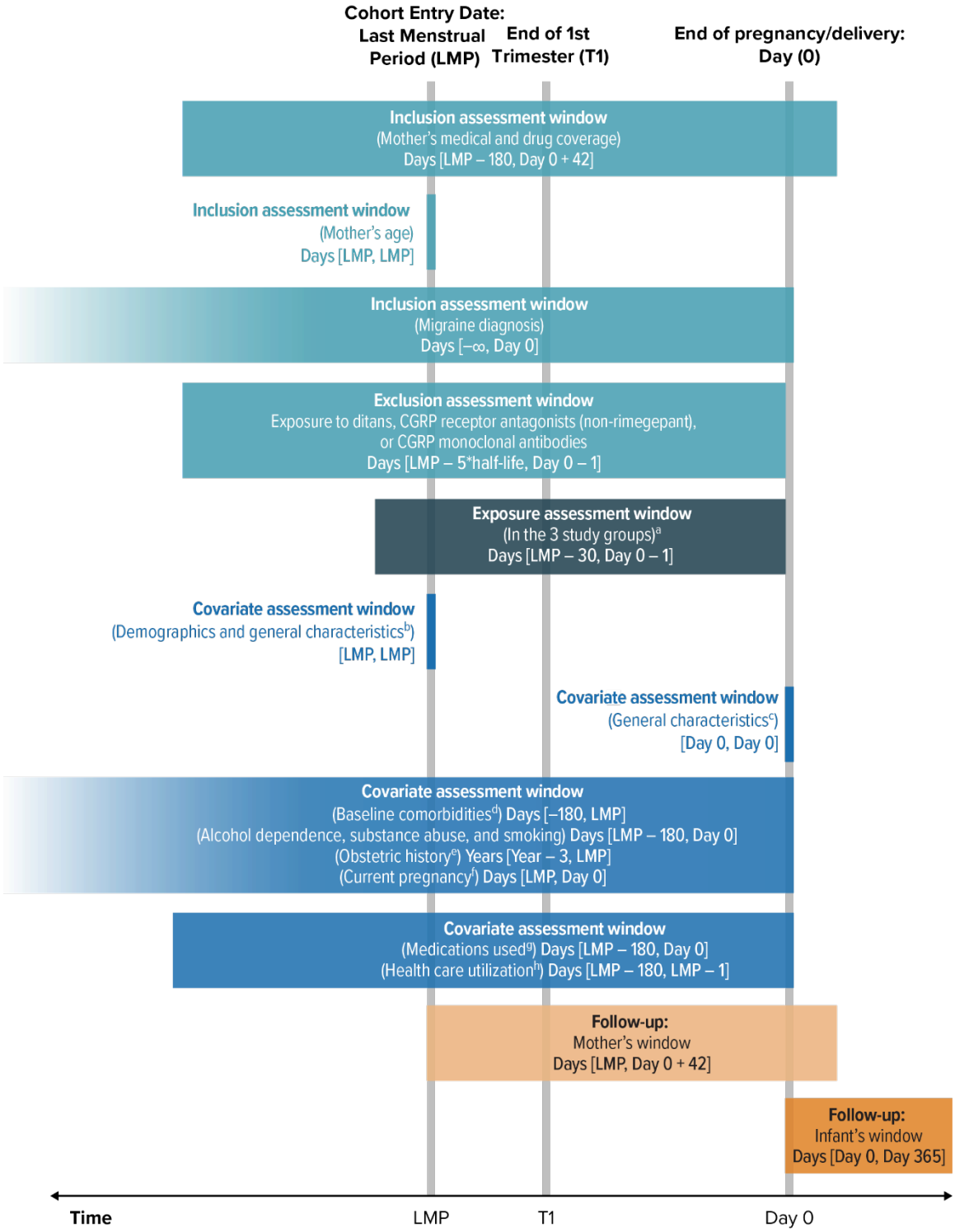
[5] Note that pregnancies without a recorded pregnancy outcome are excluded in a subsequent exclusion criterion.

9.2.5. Follow-up

The study group entry date for a pregnancy is the estimated LMP. This date is considered as the beginning of the pregnancy. The baseline period will comprise all the time available in the mother's record from January 2016 before and including the estimated LMP. The pregnancies will be followed from the estimated LMP through the end of pregnancy plus a 42-day postpartum period until a pregnancy outcome is identified. The follow-up period will vary according to the outcome evaluated. Infants will be followed from the date of birth up to 12 months or at the earliest occurrence of death, disenrollment from the data source, or end of the study period. The follow-up period will vary according to the outcome evaluated.

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

Figure 2: Design Diagram of the Rimegepant Postauthorization Safety Study



CGRP = calcitonin gene–related peptide; ED = emergency department; LMP = first day of the last menstrual period; MCM = major congenital malformation; NSAID = nonsteroidal anti-inflammatory drug; SARS-COV-2 = severe acute respiratory syndrome coronavirus 2; SGA = small for gestational age; T1 = first trimester of pregnancy;

TORCH infections = toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, herpes simplex, and Zika virus disease.

a. The exposure ascertainment window will be specific to each study outcome (see Section 9.3.1 and Table 10).
b. Age (years) at the beginning of pregnancy, race and ethnicity, duration of health plan enrollment before pregnancy, calendar year of pregnancy at the estimated date of LMP, and geographic region.
c. Calendar year of end of pregnancy.
d. Depression and bipolar disorder, anxiety and panic disorders, schizophrenia, epilepsy and seizures, cluster headache, hyperlipidemia, diabetes, hypertension, malignancy (all available data before the estimated LMP), thyroid disease, respiratory disease, including asthma, liver disease, chronic kidney disease, obesity, cardiovascular diseases.
e. Obstetric history: gravidity, parity, history of spontaneous abortions, pregnancy termination, preterm births, live births with MCM, stillbirths, SGA, gestational diabetes, and gestational hypertension in previous pregnancies.
f. Current pregnancy characteristics: multiple pregnancy, gestational diabetes, gestational hypertension; TORCH infections, and SARS-COV-2 infection.
g. Use of medications of known teratogenic potential, preventive migraine drugs (topiramate, other anti-epileptics, cardiovascular medications, antidepressants, botulinum toxin), acute migraine drugs (triptans, ergotamine derivatives, prescription NSAIDs, opioids), acute and preventive cluster headache drugs, prescription cannabinoids, antipsychotics, oral antidiabetics, insulin, antihypertensive medications, lipid-lowering drugs, antithyroid medications, antiplatelet agents, anticoagulants, anti-emetics and antinauseants, and other medications.
h. Number of office visits, telemedicine encounters, number of ED visits, and number of hospitalizations.

9.3. Variables

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

9.3.1. Exposure

The exposure of interest is rimegepant; in addition, for the primary comparator group, the exposure(s) of interest are other medications indicated for the treatment of migraine (see Section 9.2.2). Medications for acute treatment of migraine are used on an “as needed” basis to stop a migraine attack as quickly as possible. Preventive migraine medications are generally taken daily or every other day (rimegepant), and acute medications may be used concomitantly for breakthrough migraines.

The time window for ascertainment of exposure to rimegepant will include a period of 30 days before the estimated LMP until the end of pregnancy for end-of-pregnancy and infant outcomes. In a review of the Optum Research Database (ORD) for the period 01-Feb-2020 through 31-Dec-2020, 415 women aged 16-49 years had received a median of 2 rimegepant dispensings per woman (quartile 1 [Q1]-Q3, 1-3); among those with more than 1 rimegepant dispensing, the median number of days between dispensings was 31 days (Q1-Q3, 26-42). The length of the period before the estimated LMP will be further confirmed based on the analysis of patterns of rimegepant use annually during the monitoring phase as described in Section 9.7.2. A 6-month period before the estimated LMP will be used to determine the pattern of use of rimegepant. The median number of days between consecutive dispensings of rimegepant within this period will be calculated among all pregnant women with rimegepant dispensings (hereafter, “median interval”) at each annual interim analysis. The number of days between dispensings has been proposed as a preferred method to assign the duration of prescriptions when this information is not available (Enger et al., 2002; Pottegard and Hallas, 2013), as is the case for medications to be taken as needed. Hence, the median interval will be used to confirm or adjust the 30-day time window before LMP for assessing the potential exposure of the pregnancy to rimegepant in the final analyses. If adjustment is needed, the

exposure window for rimegepant will start 1 median interval before the estimated LMP and will end at the end of pregnancy. A pregnancy will be considered exposed to rimegepant if 1 or more pharmacy dispensings occur within this period (Enger et al., 2002). For the analyses of MCMs, the exposure window will include the defined time before the estimated LMP until the end of the first trimester of pregnancy (see Table 10). For analyses on spontaneous abortions or elective terminations, the exposure window will start at the defined time before the estimated LMP and extend to the end of pregnancy for pregnancies ending in spontaneous abortion or elective termination and will end at 20 gestational weeks for pregnancies that do not end in those outcomes, which roughly coincides with the period of ascertainment of these outcomes (i.e., < 20 gestational weeks). In other words, for analyses on spontaneous abortions, the exposure will be ascertained in this analysis from the start of the defined time before the estimated LMP until the earliest of the following events: end of pregnancy, disenrollment/death, or gestational Week 20. The latter condition, gestational Week 20, intends to remove immortal person-time (person-time at or after Week 20, when fetal death is defined as stillbirth and spontaneous abortion is no longer possible) (ENCePP, 2022). Table 10 (see Section 9.7.5) presents details on definitions of the exposure window for all study outcomes.

Similarly, for the primary comparator group, for medications other than rimegepant that are indicated for the acute or preventive treatment of migraine, the exposure window will include a 30-day period before the estimated LMP. An exception[6] will be botulinum toxin, for which the exposure window will include a 90-day period before the estimated LMP, in line with prescribing recommendations (BOTOX PI, 2021). The median number of days between consecutive dispensings of each type of medication (by medication category) will be obtained at each interim analysis, and the need to adjust this window for the migraine medications in the primary comparator group for the final analyses will be considered. A pregnancy will be considered exposed if a pharmacy dispensing for any of these medications occurs within the defined period for each medication category. Medications dispensed before the defined period before the estimated LMP will not be considered in determining entry into the primary comparator group.

A woman may contribute to the study with more than 1 pregnancy over the course of the study period. Eligibility criteria will be required for each pregnancy episode. Each pregnancy will be independently assessed for study eligibility (see Section 9.2.2). Furthermore, exposure status will be assessed independently for each eligible pregnancy, so that a woman may contribute to 1 group (e.g., rimegepant-exposed group) or to more than 1 study group if she had more than 1 pregnancy during the study period (e.g., 1 pregnancy to the rimegepant-exposed group and 1 pregnancy to the primary comparator group depending on the exposure of each pregnancy episode).

Exposure will be defined based on pharmacy claims information from 1 or more dispensed prescriptions (treatment initiation or continuation) with dispensing dates recorded within the defined exposure windows specific to each outcome (see Section 9.7.5, Table 10). Sensitivity analyses with varying exposure windows (e.g., by trimester) and subgroup analyses—stratified by patterns of use that correspond to acute only, preventive only, or acute and preventive use of rimegepant—will be

[6] Beginning in Interim Report 3 (2024).

conducted (see Section 9.7.6 and Section 9.7.7). Note that the median interval will not be used to ascertain second-trimester-only or third-trimester-only exposure, which are sensitivity analyses.

To validate the proposed approach to determine the exposure status, a patient survey will be conducted separately among a sample of women of childbearing age identified in the ORD who are users of rimegepant or other medications for migraine (see Annex 4). This survey will be conducted after approximately 2 years of availability of rimegepant for preventive treatment of migraine in the US. This period will allow for a relatively large number of users and a well-established use of rimegepant for acute and preventive treatment. The survey results are anticipated to be available at the time of the 2025 interim report. Additionally, rimegepant utilization patterns for acute and preventive treatment (separately) will be empirically derived from the migraine logs of participants in the pregnancy exposure registry (C4951005 [formerly BHV3000-402]).

The observed utilization patterns from these 2 sources, once they become available, will guide the classification of rimegepant users in the pregnancy outcomes study as having 1 of the 2 indications, or both.

However, until the above utilization pattern derivations become available, or if neither source provides meaningful information, the Optum electronic data on rimegepant dispensings within the 6 months before LMP will be used to classify rimegepant-exposed pregnancies. Women will be classified as having acute treatment only, preventive treatment only, both, or indeterminate treatment based on the mean number of packs dispensed per month (see Table 5). Within the 6 months before LMP, the mean number of packs dispensed per month will be calculated. Specifically, the mean number of packs dispensed per month will be calculated from the date of the first dispensing within the 6 months before LMP through LMP (for example, a woman who is dispensed a total of 4 packs of rimegepant within the 2 months before LMP will have 2 packs per month on average).

Table 5: Definitions of Rimegepant Treatment Indication

Treatment indication	Mean number of rimegepant packs dispensed per month within the 6 months before LMP[a]
Acute only	≤ 1
Preventive only	> 1 and up to and including 2
Preventive and acute (both)	> 2
Indeterminate	Patient has no rimegepant dispensings

LMP = first day of the last menstrual period.
a. Calculated from the date of the first dispensing within the 6 months before LMP through LMP.

9.3.2. Study Outcomes

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

Definitions of outcomes will be based on published, validated algorithms to the extent possible based on the available information. Study outcomes will be ascertained from outpatient and inpatient records available from the data source. To date, some published algorithms are based on *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) codes, and published validated algorithms based on ICD-10 codes in US claims data are still scant. If such

algorithms become available over the course of the study and have acceptable validation results (e.g., positive predictive value [PPV] point estimate ≥ 70%), they will be considered for use in the study final analyses. The performance of algorithms used to ascertain other study outcomes will be assessed by comparing the prevalence obtained in the secondary comparator group with published prevalence estimates from studies conducted in similar settings, prioritizing studies that used validated algorithms. If a validated algorithm becomes available over the life cycle of the study, and the performance of the original algorithm is not optimal, the research team may consider switching the algorithm.

This study plans to validate MCMs, the primary outcome of interest. The validation process will be detailed in the data validation plan, along with the strategy for estimating the target number of events for validation and the strategy for sampling events. Validation activities will be conducted before the final analyses; however, an advancement of the validation/adjudication of MCMs or other outcomes may be considered upon request by a health authority if an imbalance of the occurrence of MCMs or another study outcome is observed between the rimegepant-exposed group and the comparator group during interim analyses.

9.3.2.1. Medical Record Procurement and Adjudication

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

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

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

For each potential case, 1 medical record will be requested from 1 provider. If a medical record cannot be obtained from a primary provider, Optum will contact the alternate provider(s). Of those that are requested, approximately 70%-85% of the medical records are expected to be successfully obtained (Johannes et al., 2007; Seeger et al., 2006). Optum will contract with 2 clinical consultants with expertise in the field of clinical genetics and other relevant expertise for the adjudication of

malformations. All medical records for pregnancies with the claims-based outcomes of MCM, spontaneous abortion, fetal deaths/stillbirth, or elective termination will be reviewed for mention of MCMs, as pregnancies that do not result in live births may not have MCMs captured in medical claims. The clinicians (blinded to the maternal use/receipt of migraine treatments) will review the medical record for each potential case and adjudicate the outcomes. Each record will be independently adjudicated by 2 clinicians, and consensus will be sought for any discrepancies in adjudication results between the clinicians. Optum will work with the contracted clinicians to achieve consensus, and a third independent adjudicator will be available to arbitrate remaining discrepancies or break ties in adjudication results, if needed.

9.3.2.2. Fetal/Infant Outcomes

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

9.3.2.2.1. Primary Fetal/Infant Study Outcomes

- MCMs are the primary outcome of interest in this study.[7] Definitions and potential groupings will be based on the Metropolitan Atlanta Congenital Defects Program classification (Correa-Villaseñor et al., 2003; Scheuerle and Tilson, 2002) for the annual interim and final study analyses. In addition, MCMs will be defined based on guidelines from the European Surveillance of Congenital Anomalies programme (EUROCAT) for the final analysis (EUROCAT, 2022a).

    - Congenital cardiac anomalies that are classified as critical (i.e., cyanotic defects as well as hypoplastic left heart syndrome and pulmonary atresia) will be included among the MCM study outcome. Transient cardiac defects (i.e., patent foramen ovale, ventricular septal defect, and persistent ductus arteriosus) in term infants will also be included in the MCM study outcome because certain transient defects may be associated with maternal medication exposure in pregnancy and can vary by age of detection and/or age of resolution (Reller et al., 2008). However, transient cardiac defects in preterm births will be excluded from the definition of the MCM outcome because these malformations are often physiologically expected in preterm births and/or are found as a result of improved technology and have little clinical significance for a large proportion of cases.
    - Prematurity-related anomalies (e.g., patent ductus arteriosus, undescended testes in infants delivered at < 37 gestational weeks) and positional birth defects (e.g., torticollis, hip dislocation in infant in breech position) will not be included in the definition of MCM outcome.
    - Depending on the number of events observed, specific categories of MCMs (e.g., cardiovascular) and specific malformations (e.g., hypospadias, cleft lip with or without cleft palate, cardiac malformations) will be explored.

[7] See Table 10 for the relevant exposure window for each study outcome. The primary analysis will assess the association between first trimester rimegepant exposure and risk of MCMs.

- Algorithm A and Algorithm B will be used to identify MCMs (see Table 6) for the annual interim analyses, and only Algorithm B will be used in the final study analyses.
- Pregnancies and linked infants with identified syndromic or chromosomal anomalies (i.e., Down syndrome; trisomies 18 and 13, and other trisomies; monosomies and deletions from the autosomes; balanced re-arrangements and structural markers; Turner's syndrome, other sex chromosome abnormalities, and other chromosomal abnormalities) will not be included in the analysis of MCMs. Additionally, pregnancies and linked infants with prenatal exposure to medications with known teratogenic risk in the first trimester of pregnancy (see list of medications in Annex 3, Table 13) (Eltonsy et al., 2016) or with prenatal exposure to infections known to cause malformations will not be included in the MCM analysis (see Section 9.2.3).
- MCMs will be evaluated in live birth infants in the main analysis. A sensitivity analysis will evaluate MCMs in fetuses/infants from all pregnancies, including spontaneous abortions, fetal death/stillbirths, elective terminations, and pregnancies ending in live births; this analysis will use the Algorithm A MCM definition and search for codes for MCM around the date of the pregnancies ending in spontaneous abortions, fetal deaths/stillbirths, elective terminations, or live birth with no linked infant, and the Algorithm B MCM definition will be used for live births with infant(s) linked to maternal records. A stratified analysis of MCM (Algorithm A and B definitions) by preterm status of live birth: preterm birth and birth at ≥ 37 complete gestational weeks will be conducted (see Table 11).

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

9.3.2.2.2. Secondary Fetal/Infant Study Outcomes

Preterm birth (live birth at < 37 completed weeks of gestation). Preterm birth can be identified either from the maternal records up to 1 month after delivery or from the linked infant's record within 1 month after birth. Three algorithms will be used to identify preterm births (see Table 6), and the algorithm that shows the best performance will be used in the final analyses (see Section 9.3.2).

9.3.2.3. Pregnancy Outcomes and Pregnancy Complications

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

9.3.2.3.1. Primary Pregnancy Study Outcomes

- Spontaneous abortion [pregnancy loss at < 20 completed weeks (American College of Obstetricians and Gynecologists, 2020)]. The period for ascertainment will be the first 19 completed weeks following the estimated LMP. Abortion events with codes for ectopic or molar pregnancy will not be considered events of spontaneous abortion.
- Fetal deaths/stillbirths (≥ 20 completed weeks). Fetal death refers to a spontaneous intrauterine death of the fetus that occurs at 20 completed weeks or later in the pregnancy. Earlier fetal deaths will be considered spontaneous abortions (< 20 completed weeks).

9.3.2.3.2. Secondary Pregnancy Study Outcomes

- Elective termination. Pregnancies terminated at < 20 completed weeks, including ectopic and molar pregnancies. The reason for termination (e.g., therapeutic abortion, abnormal findings in fetus in prenatal tests, ectopic or molar pregnancy) will be ascertained to the extent to which data are available. The period for ascertainment will be the first 19 completed weeks following the estimated LMP or until abortion.
- Pre-eclampsia and/or eclampsia during pregnancy and through postpartum. The period for ascertainment will be any time during pregnancy and through 42 days after the end of pregnancy. A sensitivity analysis will be conducted restricting this analysis to pregnancies that reached 20 weeks of gestation or longer (see Section 9.7.7, Table 11).

Table 6 presents the algorithms proposed for identification of study outcomes. Currently, only some validation studies of claims-based algorithms utilizing ICD-10 codes for pregnancy and infant outcomes have been published in the literature. If additional applicable validation studies are published during the conduct of this study, claims-based algorithms for the identification of outcomes will be updated accordingly, assuming that the published algorithms for the study outcomes are shown to perform well (i.e., PPV of ≥ 70%). These claims-based algorithms will be used to identify study outcomes in lieu of medical record review, except for MCMs, for which all cases will be confirmed through medical record review (see Section 9.3.2.1).

Table 6: Algorithms for the Identification of Outcomes

Outcome	Algorithm	Pregnancies in which the outcome will be ascertained	Window for outcome ascertainment	Maternal or infant record	Validity (when available)
MCMs	Based on the definitions of the MACDP using: Algorithm A: At least 1 ICD-10-CM diagnosis code for MCM in infant claims Algorithm B: At least 2 claims with ICD-10-CM diagnosis code for MCM separated by at least 30 days in infant claims Based on the definitions of the European Surveillance of Congenital Anomalies programme using Algorithm B	Pregnancies with live birth, in linked infant (MCM Algorithm A and B): overall and by infant preterm status (Preterm Birth Algorithm A) All pregnancies in sensitivity analysis (Algorithm A for pregnancies ending in spontaneous abortions, fetal deaths/stillbirths, or elective terminations, and ending in live birth with no linked infant, and Algorithm B for pregnancies with live births, in linked infant)	From birth through 365 days after birth	Infant record	In Optum DAPI, using an ICD-10-CM algorithm, ≥ 1 claim for MCM, PPV was 44.0% (95% CI, 35.3%-52.7%); ≥ 2 claims separated by at least 30 days, PPV was 67.8% (95% CI, 55.9%-79.7%) (Chomistek et al., 2023)
SGA	≥ 1 maternal or infant ICD-10-CM diagnostic code recorded in inpatient or other therapy claims from delivery to delivery + 30 days	Pregnancies with live birth, with linked infant	From date of delivery through 30 days after delivery	Maternal and infant record	Validated algorithm based on ICD-9-CM diagnostic codes showed a PPV of 92% (95% CI, 82%-97%) (He et al., 2020)

Outcome	Algorithm	Pregnancies in which the outcome will be ascertained	Window for outcome ascertainment	Maternal or infant record	Validity (when available)
Preterm birth	Algorithm A: At least 1 maternal or infant ICD-10-CM diagnosis code for preterm birth, low birth weight, or specific conditions more common in preterm infants. Algorithm B: At least 1 maternal or infant ICD-10-CM diagnosis code for gestational age in weeks corresponding to < 37 weeks at birth. Algorithm C: Meets criteria for either Algorithm A or Algorithm B	Pregnancies with live birth, with linked infant	< 37 completed weeks of gestation Algorithm A within 0-30 days after pregnancy end date Algorithm B: Maternal codes must be within 0-7 days before pregnancy end; infant codes must be within 0-30 days after pregnancy end date	Maternal and infant record	Algorithm A is adapted from a published algorithm that included only codes designated for use in infants (Eworuke et al., 2012). This algorithm showed high PPV (> 80% for gestational age at birth of < 34 weeks) in 2 US claims databases. For the present study, the ICD-9 codes in that algorithm will be mapped to ICD-10-CM codes ICD-10-CM maternal codes for preterm delivery will also be included in this study because their ICD-9-CM equivalents have been validated in the US, with PPV of 92% (95% CI, 87%-98%) in infants' claims data and 76% (95% CI, 64%-88%) in mother's claims (Andrade et al., 2013)
Spontaneous abortion	Assignment of final pregnancy outcome as spontaneous abortion per the data source–specific pregnancy-identification algorithm (Chomistek et al., 2023)	All pregnancies	< 20 completed weeks of gestation	Maternal record	An algorithm of ≥ 1 claim with a diagnosis or procedure code for spontaneous abortion had a PPV of 84.7% (95% CI, 78.3%-91.2%) in a recent study in Optum DAPI (Chomistek et al., 2023).

Outcome	Algorithm	Pregnancies in which the outcome will be ascertained	Window for outcome ascertainment	Maternal or infant record	Validity (when available)
Fetal deaths/ stillbirths	Final pregnancy outcome of stillbirth as assigned by the data source–specific pregnancy-identification algorithm (Chomistek et al., 2023)	All pregnancies	≥ 20 completed weeks of gestation	Maternal record	An algorithm that required ≥ 20 completed weeks of gestation and at least 2 codes for stillbirth or the absence of codes for other pregnancy outcomes was validated in US claims data sources contributing to the Sentinel System. The algorithm showed a PPV of 82.5% (Andrade et al., 2021)
Elective termination	Final pregnancy outcome as termination or ectopic, or molar pregnancy per the data source–specific pregnancy-identification algorithm (Chomistek et al., 2023)	All pregnancies	< 20 completed weeks of gestation	Maternal record	Not available
Pre-eclampsia/ eclampsia	Pre-eclampsia: ≥ 1 maternal ICD-10-CM diagnostic code O14x recorded in inpatient or other therapy claims or during the delivery hospitalization or Eclampsia: ≥ 1 maternal ICD-10-CM diagnostic code recorded in inpatient or other therapy claims or during the delivery hospitalization	All pregnancies	Any time during pregnancy and through 42 days after the end of pregnancy	Maternal record	Pre-eclampsia validated algorithm based on ICD-9-CM codes showed a PPV of 82% (95% CI, 70%-91%) (He et al., 2020).

CI = confidence interval; ICD-9 = International Classification of Diseases, 9th Revision; ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM = International Classification of Diseases, 10th Revision, Clinical Modification; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; Optum DAPI = Optum Dynamic Assessment of Pregnancies and Infants; PPV = positive predictive value; SGA = small for gestational age; US = United States.

9.3.3. Other Variables

For pregnant women in each study group, the variables listed below will be ascertained using information available in the mother's medical record during the period before pregnancy and during pregnancy. The period for ascertaining baseline characteristics will be limited by the period of enrollment in the health care plan. For most variables, no missing values are expected. For variables related to patients' medical history or drug exposure, the absence of a diagnosis code for a condition is interpreted as the absence of the condition, and the absence of medication claims is interpreted as the absence of exposure to those medications. Obesity, smoking, alcohol misuse, and drug misuse are ascertained through codes (including proxies) and may be under-recorded (see Section 9.7.4). Race and ethnicity will be imputed using an algorithm/model based on the mother's given name, last name, and place of residence (census ZIP code [ZIP+4 digits]). The variables listed below were selected to provide a general description of the characteristics of the study groups and to explore potential confounding. The definitions and period of ascertainment for these variables are described in Annex 3, Table 14.

Demographic and general characteristics:

- Age (years) at the beginning of pregnancy
- Race and ethnicity (Asian, Black, Hispanic, White, Other, and Unknown) will be estimated by an algorithm/model that incorporates zip code and name (Lin et al., 2020)
- Duration of health plan enrollment before pregnancy
- Calendar year of pregnancy at the estimated date of LMP
- Calendar year of end of pregnancy
- Geographic region (Northeast, West, Midwest, South, unknown)

Prior history of medical conditions will be identified based on ICD-10-CM diagnosis codes within a look-back period of 6 months before the estimated LMP and including LMP date, except where indicated, and through the end of pregnancy where indicated (see Annex 3, Table 14):

- Depression and bipolar disorder
- Anxiety and panic disorders (generalized anxiety disorder, panic disorder with and without agoraphobia, social anxiety disorder)
- Obsessive-compulsive disorder
- Schizophrenia
- Epilepsy and seizures
- Alcohol misuse, using proxies based on diagnoses and specific treatments
- Drug misuse, using proxies based on diagnoses and specific treatments
- Hyperlipidemia
- Diabetes
- Hypertension
- Malignancy, within a look-back period that can extend from January 2016 to and including LMP date
- Thyroid disease
- Respiratory disease, including asthma
- Liver disease
- Chronic kidney disease
- Obesity, using diagnoses and specific treatments or procedures, as available in medical claims

- Smoking, use proxies based on diagnoses and specific treatments, as available in medical claims
- History of cardiovascular diseases, including myocardial infarction, transient ischemic attack, ischemic stroke, ischemic heart disease, angina, heart failure, cardiac arrhythmia, hemorrhagic stroke, peripheral vascular disease
- Pain conditions
- Cluster headache

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

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

- Gravidity, the number of pregnancies before the current pregnancy
- Parity, the number of deliveries or C-sections before the current pregnancy
- Spontaneous abortions, history of spontaneous abortions in previous pregnancies
- Pregnancy termination, history of previous terminated pregnancies
- Preterm births, history of preterm births before the current pregnancy
- Live births with MCMs, history of pregnancies with live births with MCMs before the current pregnancy
- Stillbirth, history of pregnancies with stillbirth before the current pregnancy
- SGA, history of deliveries with codes indicative of SGA
- Gestational diabetes, gestational diabetes during pregnancy(s) before the current pregnancy
- Gestational hypertension, gestational hypertension during pregnancy(s) before the current pregnancy

Comedication use will be ascertained separately in the 6 months before the estimated LMP and during pregnancy. Medications will be identified based on National Drug Codes, or HCPCS codes, as applicable (see Annex 3, Table 14):

- Use of medications of known teratogenic potential (see Annex 3, Table 13)
- Use of prescription cannabinoids
- Preventive cluster headache drugs
- Acute cluster headache drugs
- Antidepressants
- Antipsychotics
- Oral antidiabetics
- Insulin
- Antihypertensive medications
    - Calcium channel blockers
    - Angiotensin-converting enzyme inhibitors
    - Angiotensin II antagonists
- Lipid-lowering drugs
- Antithyroid medications

- Antiplatelet agents
- Anticoagulants
- Anti-emetics and antinauseants
- Other medications associated with the medical conditions identified previously

Use of preventive migraine drugs will be ascertained separately in the 6 months before and during pregnancy: topiramate, other anti-epileptics, beta-blockers, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitor, and botulinum toxin. The list of specific medications is shown in Annex 3, Table 12.

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

Use of acute migraine drugs will be ascertained separately in the 6 months before and during pregnancy: triptans, ergotamine derivatives, prescription NSAIDs, aspirin, acetaminophen, and opioids. The list of specific medications is shown in Annex 3, Table 12.

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

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

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

Characteristics of the current pregnancy:

- Multiple pregnancy
- Gestational diabetes
- Gestational hypertension
- TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus [CMV], herpes simplex, and Zika virus disease) during pregnancy
- SARS-COV-2 infection during pregnancy

9.4. Data Sources

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

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

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

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

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

- Use of designated claims forms (e.g., physicians use the Health Care Financing Agency 1500 form, and hospitals use the UB-04 or UB-92 form)
- ICD-9 codes
- ICD-10 codes
- CPT codes
- HCPCS codes
- Cost information
- De-identified patient and provider codes

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

- National Drug Code
- Drug name
- Dosage form
- Drug strength
- Fill date
- Days of supply
- Cost information
- De-identified patient and prescriber codes

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

This study will employ the Optum Dynamic Assessment of Pregnancies and Infants (DAPI), a proprietary process that includes a set of capabilities and established algorithms that is applied to claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link mothers' and infants' data in an ongoing manner within the ORD (Bertoia et al., 2022). The algorithms are based on a combination of validated algorithms as reported in the literature and clinical input. Estimates from recent years show that in total, over 1 million pregnancies have been identified from 01-Oct-2015 through 30-Sep-2020 (Bertoia et al., 2022).

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

Approximately 80,000-100,000 pregnancies are identified each year within the database. Of these pregnancies, approximately 84% can be linked to an infant (Bertoia et al., 2022). These linkages enable proactive monitoring of pregnancy outcomes to ascertain a range of outcome-specific risks associated with drug exposure during pregnancy. This linkage has been used to address regulatory questions by pharmaceutical companies about the effects of drugs on pregnancy (Cole et al., 2007a; Cole et al., 2007b).

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

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

9.5. Study Size

With a ratio of 1:3 for exposed to unexposed pregnancies, the minimum number of exposed pregnancies to provide 80% probability to reject the null hypothesis (RR = 1.0) at the alpha = 0.05 level for RRs of 2, 2.5, 3 and 4 is presented in Table 7 for each study outcome. For the primary outcome MCMs with a prevalence of 3% in unexposed pregnancies, a study size of 464 rimegepant-exposed pregnancies with linked infants (and 1,392 in each comparator group) would provide 80% power to reject the null hypothesis if the true population RRs were 2. If the true population RRs were 2.5, a study size of 233 exposed pregnancies with linked infants (and 699 in each comparator group) would provide 80% power to reject the null hypothesis.

Table 7: Estimated Number of Rimegepant-Exposed Subjects Needed to Have an 80% Probability of Rejecting the Null Hypothesis (RR = 1.0) at the *P* = 0.05 Level for True Relative Risks of 2, 2.5, 3, and 4

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

MCM = major congenital malformation; RR = relative risk; SGA = small for gestational age.
Note: The numbers of rimegepant-exposed subjects represent the number of exposed pregnancies needed for the maternal outcomes (abortion, stillbirth, elective termination, pre-eclampsia/eclampsia) or the number of mother-infant pairs for live birth outcomes (MCMs, SGA, preterm birth).
a. Assuming 80% power, alpha = 0.05, a ratio of exposed to unexposed subjects of 1:3. Calculations were performed using PS: Power and Sample Size Calculation version 3.1.6, October 2018 (Dupont and Plummer, 1990).
b. Primary outcome.
c. Centers for Disease Control and Prevention (CDC) (2008).
d. Jensen et al. (2019).
e. Secondary outcome.
f. Martin et al. (2021).
g. Data provided by Optum (Optum Research Database, October 2015 through September 2020).
h. Kortsmit et al. (2020).
i. Fingar et al. (2017).

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

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

Table 8 presents the minimum detectable risk estimates for each of the study outcomes with a study size of 464 rimegepant-exposed pregnancies with linked infants and 1,392 unexposed pregnancies with linked infants.

Table 8: Minimum Detectable Risk Estimate for Each Study Outcome With the Target Study Size

Outcome	Prevalence of outcome	Minimum detectable relative risk with 464 rimegepant-exposed pregnancies and linked infants[a]
MCMs[b]	3%[c]	2.00
SGA[b]	11.1%[d]	1.46

Preterm birth[c,e]	10.23%[f]	1.48
Abortion (spontaneous and therapeutic)[b]	16%[g]	1.36
Stillbirth[b]	0.4%[g]	4.66
Elective termination[e]	11.3 per 1,000 women aged 15-44 years[h]	2.83
Pre-eclampsia/eclampsia[e]	4.7%[i]	1.77

MCM = major congenital malformation; SGA = small for gestational age.
a. Assuming 80% power, alpha = 0.05, a ratio of exposed to unexposed subjects of 1:3. Calculations were performed with PS: Power and Sample Size Calculation version 3.1.6, October 2018 (Dupont and Plummer, 1990).
b. Primary outcome.
c. Centers for Disease Control and Prevention (CDC) (2008).
d. Jensen et al. (2019).
e. Secondary outcome.
f. Martin et al. (2021).
g. Data provided by Optum (Optum Research Database, October 2015 through September 2020).
h. Kortsmit et al. (2020).
i. Fingar et al. (2017).

The actual study size will depend on medication uptake in the study data source, as well as on the observed percentage of live births among the study pregnancies and success of mother-infant record linkage. From previous experience with Optum DAPI, over 80% of pregnancies may result in live births, and approximately 84% of those pregnancies were linked to infant records (Bertoia et al., 2022). In the period from October 2015 through September 2020, 1,030,874 pregnancies were identified in the ORD, including 821,536 pregnancies (80%) with an observed outcome (i.e., evaluable pregnancies). These pregnancies comprised 626,426 live births (76%) and 195,110 non-live births (24%). A total of 209,338 pregnancies exhibited no known outcomes that would conform to the primary or secondary outcomes at the time of the query (mostly because the woman disenrolled or the pregnancy was still ongoing). From February 2020 through 31-Dec-2020, 627 women had at least 1 dispensing of rimegepant in the ORD. Of these women, 415 were aged 16 to 49 years and had a total of 864 dispensings collectively, with a median of 2 dispensings per woman.

The feasibility of meeting the target study size will be assessed annually during the monitoring phase and reported in the annual interim reports. Yearly counts, using all inclusion and exclusion criteria defined in the protocol for entry into the study groups, will inform whether the observed accrual of rimegepant-exposed pregnancies is sufficient to achieve the target study size. The accrual of rimegepant-exposed pregnancies will be examined at each step of the implementation of eligibility criteria in the annual interim reports. At the 2025 interim report, expected to include over 3 years of accrual of pregnancies in the study, if the projection indicates that the study size will be below the target size, in consultation with the FDA, a potential modification of the eligibility criteria will be considered to increase the study size. Specifically, the exclusion criterion related to use of ditans or CGRP monoclonal antibodies in pregnancy will be reassessed. Additionally, a potential revision of the algorithm to identify women with migraine diagnosis may also be considered if substantial rimegepant-exposed pregnancies are being excluded due to not meeting the criteria for the migraine algorithm, and/or the prevalence of migraine in the study population is shown to be lower than population-based prevalence estimates (see Section 9.2.1.2). Finally, if deemed necessary, and in consultation with the FDA, the inclusion of additional data sources to achieve the target study size will also be considered and discussed in the 2025 interim report.

9.6. Data Management

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

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

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

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

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

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

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of 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.

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

9.7.1. Study Groups

The study groups are summarized in Table 9.

Table 9: Study Groups

	Exposed	Primary comparator group	Secondary comparator group
Study group definition	Pregnancies in women with migraine and exposure to rimegepant	Pregnancies in women with migraine exposed to other medications indicated for the treatment of migraine	Pregnancies in women without migraine
Migraine diagnosis	Required	Required	No diagnosis recorded in all available data in the period before the beginning of pregnancy or during pregnancy
Drugs	Required: Use of rimegepant within defined period of 30 days before the estimated LMP or any time during pregnancy[a]	Required: No use of rimegepant within defined period of 30 days before the estimated LMP or any time during pregnancy Use of medications other than rimegepant that are indicated for the treatment of migraine within the defined period of 30 days before pregnancy (90 days for botulinum toxin) or any time during pregnancy[a]	No use of rimegepant within the defined period of 30 days before the estimated LMP or any time during pregnancy[a]
	No use of ditans, CGRP receptor antagonists other than rimegepant, or CGRP monoclonal antibodies within a 5–half-life time window before the estimated LMP and any time during pregnancy[a]		

CGRP = calcitonin gene–related peptide; LMP = first day of last menstrual period; MCM = major congenital malformation.
a. See Table 10 for the relevant exposure window for each study outcome. The primary analysis will assess the association between first trimester rimegepant exposure and risk of MCMs.

9.7.2. Descriptive Analyses

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

The study groups (exposed group, primary comparator group, and secondary comparator group) will be characterized based on the covariates listed in Section 9.3.3.

For Objective 1, the use of medications for migraine will be analyzed in the 6 months before the estimated LMP, including the number of users; mean, standard deviation, median, and interquartile range of the number of dispensings; the number of days between consecutive dispensings for each medication; the distribution of pregnancies exposed to migraine medications in various pre-pregnancy and pregnancy periods; the distribution of pregnancies exposed to rimegepant by potential acute, preventive, acute and preventive, or indeterminate treatment indication; and the distribution of pregnancies in the rimegepant-exposed and the primary comparator group by type of exposure to migraine medications before and during pregnancy (i.e., exposure to acute migraine medications only, preventive migraine medications only, and

both acute and preventive migraine medications). These analyses will be included in the annual interim and final reports.

For Objective 2, a description of the cohort attrition by eligibility criteria, time interval between consecutive pregnancy episodes in the same woman, selected characteristics of the pregnancies in each study group, and frequency of the study outcomes will be reported for each study group in the annual interim report. Analyses based on claims-identified cases, including outcomes that have unvalidated algorithms and outcomes that have validated algorithms, will be presented. For the primary outcome of MCM, algorithms A and B (see Table 6) will be used to estimate the prevalence in live births overall and by preterm status in the annual interim analyses. In the final analysis, in addition to the prevalence of MCMs (Algorithm B), the total prevalence of MCMs as defined by EUROCAT will also be presented (EUROCAT, 2022b).

The annual interim report will include an assessment of the extent to which the study population—pregnant women with migraine identified in a US data source—is representative of pregnant women with migraine in EU countries. This will be based on assessment of the distribution of key characteristics of these populations presented in tabular format. Sources for the characteristics of pregnant women with migraine in EU countries will include publications from the ConcePTION Consortium (Dudman et al., 2022) and other relevant sources that may become available.

9.7.3. Comparative Safety Analysis

For Objective 3, the safety comparative analyses, propensity score methods will be used. Each pregnancy will be assigned a propensity score, a measure of the probability of receiving rimegepant versus a comparator drug (or no drug) given that patient's characteristics.

Propensity scores will be estimated using logistic regression. The model will include only covariates that could act as potential confounders as independent variables; the dependent variable will be rimegepant use/nonuse ascertained from the 30 days before the estimated LMP to the end of the first trimester of pregnancy. Only covariates assessed during baseline (i.e., before the estimated LMP) and known (or highly suspected) to be confounders will be included in the propensity score model. A missing category for the potential confounders, when applicable, will be included when building the propensity score model. Variables for the propensity score modeling will include prespecified variables from Section 9.3.3, including demographic and general characteristics, prior history of medical conditions, prior obstetric history, comedication before LMP, use of preventive migraine drugs before LMP, use of acute migraine drugs before LMP, and health care utilization. Characteristics of and medications used during the current pregnancy will not be included in the propensity score model. In addition, to ensure that important potential confounders are not inadvertently omitted, the most common diagnoses given, procedures administered, and drugs dispensed among the rimegepant-exposed group members will be identified using stepwise logistic regression. The list of these additional covariates will be reviewed by study researchers, and only those covariates that are known risk factors of adverse pregnancy/infant outcomes will be considered for inclusion in the propensity score model. Those covariates that are correlates of rimegepant use but are not risk factors for the outcomes (and therefore not confounders) will be removed from consideration. As some prespecified covariates may be closely correlated with the data-driven identified variables, correlations between prespecified and the data-driven defined covariates will be calculated. For variable pairs that are highly correlated (e.g., correlation > 0.9), 1 will be eliminated (retaining prespecified covariates where possible). In addition, univariate c-statistics will be evaluated for

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

A single propensity score model predicting rimegepant exposure from 30 days before the LMP through the end of the first trimester will be used for all outcomes in comparisons of rimegepant-exposed pregnancies and pregnancies in the primary comparator group, and another propensity score model will be used for all outcomes in comparisons of rimegepant-exposed pregnancies and pregnancies in the secondary comparator group.

Rimegepant-exposed pregnancies will be matched separately to up to 3 pregnancies in each of the comparator groups on propensity score. Matching will be done based on a digit-based, greedy, nearest-neighbor matching process, in which exposed patients are matched, without replacement, to unexposed patients with the same propensity score at a given level of precision defined by the number of digits of the propensity score. When no further matches are available at a given level of precision, the number of digits is sequentially reduced, until a maximum allowable caliper of 0.1. This method has been shown to be an efficient approximation of nearest-neighbor matching. The caliper may be decreased in the case of insufficient balance following matching (Rassen et al., 2012).

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

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

Because the matching can result in the exclusion of some (unmatched) rimegepant-exposed pregnancies, alternative analysis methods may be considered. Namely, propensity scores (in continuous or categorical form) may be included in the outcome models or used in inverse probability of treatment weights (Desai and Franklin, 2019). These approaches can achieve similar levels of covariate control as matching, without the risk of excluding pregnancies due to a lack of suitable matches, but are broadly expected to produce similar results (Austin, 2011).

Inverse probability of treatment weighting will be the first alternative method to explore whether propensity score matching appears not to be feasible or appropriate. In that situation, stabilized weights will be estimated following specifications described by Hernán and Robins (2020), and weights will be trimmed at the 1st and 99th percent as described by Stuart (2010). These weights will then be used in weighted outcome regression models.

Comparative analyses for the primary and secondary outcomes will be conducted in the study groups for the final study analyses when the target study size has been attained and results will be reported in the final study report. Analyses based on claims-identified cases, including outcomes that have unvalidated algorithms and outcomes that have validated algorithms, will be presented. However, the primary comparative analyses for MCM will include only MCM outcomes that have been confirmed via medical record review or identified via validated algorithms. Table 10 presents the measures of association planned for each outcome. Regression models will be used to compare pregnant women with migraine exposed to rimegepant during the exposure window with women in the primary comparator group and in the secondary comparator group. Point estimates and 95% CIs from crude analyses within the matched study groups will be presented.

9.7.4. Missing Data

Using automated health care data, missing data for exposure, outcome, comorbidities, and comedications are expected to be minimal. In the presence of records for a given medical condition, it is assumed that the medical condition is present; in the absence of such records, it is assumed that the medical condition is absent. Otherwise, where relevant, the percentage of missing data will be reported (e.g., outcome data may be missing due to health plan disenrollment or infants not linked to maternal data, mother's geographic region of residence). Information on body mass index, smoking, drug misuse, and alcohol consumption is not recorded in health care claims databases. However, obesity will be ascertained through diagnosis codes for obesity–related disorders; alcohol consumption through diagnosis codes for alcohol misuse, dispensings of medications indicated for treatment of alcohol misuse, and alcohol-related disorders; drug misuse through diagnosis codes for drug misuse; and smoking will be defined based on the use of smoking-cessation drugs and smoking-related diagnoses. It is acknowledged that this will underestimate the prevalence of obesity, alcohol misuse, and smoking. Race and ethnicity are not available in Optum DAPI and will be imputed using an algorithm/model based on the mother's given name, last name, and place of residence (census ZIP code [ZIP+4 digits]).

9.7.5. Statistical Analyses

A summary of the analyses proposed for each outcome is presented in Table 10.

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

Table 10: Statistical Analyses of Study Outcomes

Outcome	Measure of frequency (objective 2)	Measure of association (regression model) (objective 3)	Timing of outcome ascertainment	Timing of exposure ascertainment[a]	Unit of analysis
MCMs	Prevalence	RR (log-binomial regression)	From birth through 365 days after birth	30 days before LMP up to and including first trimester of pregnancy	Main analysis: infants from live births. Sensitivity analysis:

Outcome	Measure of frequency (objective 2)	Measure of association (regression model) (objective 3)	Timing of outcome ascertainment	Timing of exposure ascertainment[a]	Unit of analysis
					fetuses/infants from all pregnancies, including spontaneous abortions, fetal deaths/stillbirths, elective terminations, and pregnancies ending in live births
SGA	Prevalence	RR (log-binomial regression)	From date of delivery through 30 days after delivery	30 days before LMP or any time during pregnancy	Live births
Preterm births	Prevalence	RR (log-binomial regression)	< 37 completed weeks of pregnancy	30 days before LMP up to the earliest of end of 36 weeks of pregnancy (not including Week 37) or the end of pregnancy	Live births
Spontaneous abortions	Prevalence	RR (log-binomial regression)	< 20 completed weeks of pregnancy	30 days before LMP up to the earliest of end of 19 weeks of pregnancy (not including Week 20) or the end of pregnancy	Pregnancy
Fetal deaths/ stillbirths	Prevalence	RR (log-binomial regression)	≥ 20 completed weeks of pregnancy	30 days before LMP or any time during pregnancy (i.e., before the time of fetal death)	Pregnancy
Elective terminations	Prevalence	RR (log-binomial regression)	< 20 completed weeks of pregnancy	30 days before LMP up to the earliest of end of 19 weeks of pregnancy, or end of pregnancy if before the end of 19 weeks	Pregnancy
Eclampsia/pre-eclampsia	Prevalence	RR (log-binomial regression)	At any time during pregnancy and through 42 days after the end of pregnancy	30 days before LMP or any time during pregnancy	Pregnancy

LMP = first day of last menstrual period; MCM = major congenital malformation; RR = relative risk; SGA = small for gestational age.

a. Exception for botulinum toxin: start of exposure ascertainment is 90 days before LMP.

9.7.6. Subgroup Analyses

Possible stratifications (depending on counts) may include strata of maternal age (e.g., < 18 years, 18-34 years, ≥ 35 years), calendar year, and others (see Table 11). Based on the observed pattern of rimegepant use, using information on the number of dispensed prescriptions, days' supply and days between dispensings, rimegepant-exposed pregnancies will be grouped by whether women received rimegepant for acute treatment only, preventive treatment only, or for both, and subgroup analyses will be conducted for all study outcomes.

9.7.7. Sensitivity Analyses

Rimegepant is indicated for the acute treatment of migraine and for the preventive treatment of episodic migraine in adults. The recommended dose for the acute treatment is 75 mg taken orally, as needed, and the maximum dose in a 24-hour period is 75 mg. The recommended dose for the preventive treatment is 75 mg every other day. Based on information from claims for pharmacy dispensings, determining the time of exposure and whether the exposure occurred is uncertain. Pregnant patients may take medication during pregnancy that was prescribed and dispensed before the start of pregnancy. Even if medication was prescribed and dispensed during pregnancy, it is not possible to verify if the patient took the medication. Three sensitivity analyses are planned in relation to the definition of the exposure window and the timing of exposure (see Table 11).

Moreover, several of the medications used for the treatment of acute migraine are available over the counter, and such use is not captured in health care databases based on administrative claims. Lack of data on over-the-counter medications is a limitation common to all observational studies using this type of data source. Data on the prevalence of use of over-the-counter medications for acute migraine collected in the Pfizer study (C4951005 [formerly BHV3000-402]) will be used in the present study to inform a quantitative bias analysis; this bias analysis will provide information on the robustness of the study findings in relation with this source of exposure misclassification.

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

Other sensitivity analyses are planned in relation to study outcome ascertainment. Table 11 presents both subgroup and sensitivity analyses.

Table 11: Subgroup and Sensitivity Analyses

Topic	Application	Analysis
Exposure	All outcomes	Redefine the exposure window using the 75th percentile of the time between consecutive prescriptions to define the time window before the estimated LMP and through the end of pregnancy
Exposure	All outcomes	Stratify by timing of exposure (by trimester of exposure, any time during pregnancy)
Exposure	All outcomes	Stratify by rimegepant patterns of use that correspond to acute treatment only, preventive treatment only, or both acute and preventive treatment
Exposure	All outcomes	Stratify by type of medication received in the primary comparator group (by medication category and by acute and preventive medications)

Topic	Application	Analysis
Exposure	MCMs	Restrict the rimegepant-exposed group to pregnant women with 2 or more dispensings in the 30-day period before the estimated conception and through pregnancy
Exposure	All outcomes	Quantitative bias analysis of exposure misclassification related to the use of over-the-counter medications to treat migraine
Outcomes	All outcomes	Stratify by maternal age at beginning of pregnancy (< 18 years, 18-34 years, ≥ 35 years)
Outcomes	MCMs	Stratify by preterm status of live births: preterm birth or birth at ≥ 37 complete gestational weeks
Outcomes	MCMs	Restrict outcome to inpatient diagnoses
Outcomes	MCMs, SGA, and preterm birth outcomes	Restrict analysis to singleton pregnancies
Outcomes	SGA and preterm birth outcomes	Restrict analysis to singleton pregnancies resulting in live births without MCMs
Outcomes	MCMs	Analysis including fetuses/infants from all pregnancies: pregnancies ending in fetal deaths/stillbirths, spontaneous abortions, elective termination, and live births
Outcomes	Pre-eclampsia/eclampsia	Restrict analysis to pregnancies that reached 20 gestational weeks or greater
Outcomes	All outcomes	Restrict analysis to the first observed pregnancy per woman in the study groups

LMP = first day of last menstrual period; MCM = major congenital malformation; SGA = small for gestational age.

9.8. Quality Control

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

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

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

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

The ORD contains data derived from claims submitted by providers and pharmacies to obtain payment for health care services rendered, data to track plan membership for premium billing, and provider data to track participating physicians who have contracts with health plans to provide services. The underlying administrative data are routinely captured, verified, automated, and de-identified. The data undergo regular audits and QC procedures by the insurer and are updated monthly. Although the health insurance claims data represent financial transactions and are not research records, the financial transactions related to the services provided create

financial incentives to record them correctly and fully, so the billable medical services represented in the database are likely to be complete. The validity of this claims research database for epidemiologic research (as compared with data abstracted from medical records) has been established (Dore et al., 2011; Eng et al., 2012; Loughlin et al., 2010; Quam et al., 1993).

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

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

9.9. Limitations of the Research Methods

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

The diagnosis of migraine will be based on a claims-based algorithm used in previous studies. Although formal validation of this algorithm is not planned, an indirect validation process can be conducted by calculating the estimated prevalence of migraine in the study and evaluating whether the estimated prevalence is in line with existing reports (Hoffman et al., 2019; Wood et al., 2021; Yusuf et al., 2018). Additionally, a potential revision of the migraine algorithm may be considered if a substantial number of rimegepant-exposed pregnancies are being excluded from the study due to not meeting the criteria for migraine algorithm and/or the prevalence of migraine in the study population is shown to be below that expected from population-based estimates.

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

MCMs are more easily identified in live infants with successful mother-infant linkage (as will be done for the main analysis) than in pregnancies ending in other outcomes or in which the infant records could not be linked to the maternal records (sensitivity analysis). This is a limitation of all research on MCMs, given that autopsies are often not performed on spontaneous abortions, stillbirths, or pregnancy terminations (and the presence of MCMs would not be known to health care providers or the mother and family), and more frequently in studies that use existing data sources (in which underrecording of known MCMs in fetuses may occur). In a sensitivity

analysis, the research team will try to identify these malformations by looking for MCM codes around the time of the fetal demise or delivery of a nonlinked infant.

Left censoring may be a limitation for the ascertainment of baseline characteristics, such as prior comorbidities and past obstetrical history. The shorter the look-back period, the more likely it is that the baseline prevalence is underestimated, and this is most likely to occur for chronic conditions, which may have been recorded a long time before the study period begins. All the available information in the electronic record of the mother will be used to ascertain these variables to minimize left censoring. However, availability of information will depend on the time of enrollment of pregnant women in the health plans. This study has design features to minimize the risk of immortal person-time bias, although some immortal time bias may remain. The windows for exposure ascertainment are specific to each outcome, with the end of the exposure ascertainment window being the end of the at-risk period for each specific outcome (e.g., 20 weeks of pregnancy for spontaneous abortions and elective terminations, 37 weeks of pregnancy for preterm births) (ENCePP, 2022).

Prescription dispensing claims may not reflect actual exposure because only pharmacy dispensing information is captured, not actual patient use. Due to the type of medication under study (acute treatment of migraine or preventive treatment), the actual exposure will be uncertain because rimegepant and other medications indicated for the acute treatment of migraine are medications used on demand (e.g., during an episode of migraine). The complexity in migraine is that acute medication is taken “as needed” per the product label, and instructions for rimegepant are for use of a maximum dose of 75 mg (1 tablet) in a 24-hour period. For rimegepant, each dispensing constitutes 1 pack of 8 orally disintegrating tablets, and the estimated number of days for use is 30 days for acute treatment. For preventive treatment, given the recommended dose, it is anticipated that 2 packs will be used in a 30-day period. Rimegepant utilization will be assessed during the monitoring phase, the number of dispensings and the time interval between dispensings will help to determine if the 30-day window before the estimated LMP for exposure ascertainment is adequate. In the current study, it was assumed that a patient is exposed at the time of the dispensing of the medication prescription. This might represent an overestimation of the true exposure. However, this overestimation would be nondifferential between triptans and other medications indicated for acute treatment of migraine and rimegepant users. The observed pattern of use of rimegepant based on information from dispensings will be used to identify treatment as acute only, preventive only, or both acute and preventive treatment. Sensitivity analyses with varying definitions of exposure and subgroup analyses by presumed acute and preventive use will be conducted. In addition, a patient survey in a sample of women drawn from the same source population as the study population is planned in order to collect information on how rimegepant and other medications for migraine are used (see Annex 4). The survey aim is to validate the proposed approach to determine the exposure status in the current study.

Furthermore, some medications used for the treatment of migraine are available over the counter and are used to treat other forms of pain in addition to migraine. Although it is possible that over-the-counter use is mentioned in medical records for some patients, it is very plausible that most over-the-counter medication use is not recorded at all. Misclassification of over-the-counter drug use is common to all research using automated health care data. Efforts will be in place to identify exposure to these medications from other sources. The companion pregnancy registry study addressing postmarketing requirement 3799-6 (Pfizer study C4951005 [formerly BHV3000-402]) will collect information on medications used for migraine, including prescription and over-the-counter medications, for both the exposed and comparator groups. Information will be collected through a mobile app (much akin to the patient survey that FDA

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

In addition, in studies evaluating the risk of exposure during pregnancies, the accurate identification of the beginning of pregnancy is crucial because some outcomes are occurring at specific time points of the pregnancy (e.g., during the first trimester). In the current study, the start of pregnancy will be estimated using the most appropriate and valid method (Hornbrook et al., 2007; Margulis et al., 2015; Matcho et al., 2018).

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

Sufficient uptake of rimegepant, a recently approved drug in the US, will be needed to conduct the study and to have conclusive results. A period of inclusion will be required to accrue enough exposed patients (currently expected to be 2020-2027). Annual interim analyses will inform the progress toward the target size. With a small study size, some study outcomes with very low incidence might not be detected, or estimates will be of limited precision. The study size in this study might not be sufficient to identify an increased risk of specific MCMs. One possible exception is cardiac malformations, because they are the most frequent type of malformations (EUROCAT, 2022c).

Rimegepant is a recently approved medication compared with other more established migraine therapies such as triptans, used as comparators in this study. This study will include the time period when rimegepant was first approved, and thus, the use of rimegepant may change rapidly over time, and the specific profile and severity of early users may evolve when the drug becomes more established and its use increases (Gagne et al., 2013). Furthermore, health plan coverage for rimegepant may require prior authorization or a “step-through” therapy (e.g., failure of triptans), so patients in the rimegepant-exposed group may have more severe forms of migraine than patients in the comparator groups.

This study is being conducted in a health insurance claims database and will only collect information in a subset of the target population representing a well-defined and enumerated population in the US. This database is composed of employed individuals and their dependents; thus, the pregnancies observed within the database tend to be among women who are somewhat older than the US population as a whole. The women in the database are also geographically, racially, and ethnically diverse (Bertoia et al., 2022). The age distributions of pregnant women with migraine in the US and in European populations are comparable (Amundsen et al., 2019; Skajaa et al., 2019; Wood et al., 2021), and migraine management guidelines in the US and Europe have similar recommendations (American Headache Society, 2019; Eigenbrodt et al., 2021; Marmura et al., 2015). Although pregnant women with migraine in the US and the EU may differ in terms of migraine treatments received (reflecting drug availability, access to health care, and patient and clinician preferences), and risk factors for the study outcomes (e.g., lifestyle factors, prevalence of comorbidities), the measures of association that this study will estimate are anticipated to be broadly applicable to both regions. Throughout the present study, an assessment

of representativeness of this US-based study population regarding the target population in EU countries will be included in the annual interim reports. Key characteristics of the US study population and of pregnant women with migraine from EU countries will be described in a tabular format. Sources for the EU population will include research conducted by the ConcePTION Consortium (Dudman et al., 2022) or other research groups. Prevalence rates of MCMs available from well-established surveillance systems (i.e., Metropolitan Atlanta Congenital Defects Program and EUROCAT) will be used as a reference for the findings from the present study.

Information on lifestyle variables (such as smoking; use of alcohol, cannabinoid-related products, or illicit drugs; and body mass index), as well as socioeconomic status, is not usually available in claims databases. Because these variables can be potential confounding factors or effect modifiers, indirect identification can be made through diagnosis codes for obesity and/or through dispensing drugs for smoking or alcohol disorders. In any case, the identification of these variables will likely be underestimated. Additionally, information on race and ethnicity is incomplete or not available in claims databases. An algorithm that imputes the race and ethnicity variable will be used in this study; however, this method presents some limitations. It is not possible to separate race from ethnicity with this algorithm. Research conducted on the concordance of the imputed variable with information contained in electronic health records has shown a good PPV for White race, but it does not work optimally for other racial and/or ethnic groups (Lin et al., 2020). Misclassification of race and ethnicity is likely to occur, and with increasing geographic mobility and the growing number of multi-racial and multi-ethnic families, the probability of misclassification may increase.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

This study includes 3 forms of data collection methods: the main analysis will only use structured data; the outcome validation will involve human review of unstructured data, and the survey component (see Annex 4) will involve primary data collection. Considerations for protection of human subjects regarding each of these 3 data collection methods have been summarized in separate sections below.

10.1. Patient Information

10.1.1. Structured Data Analysis (Main Analysis; Optum Research Database)

This study's main analysis involves data that exist in de-identified structured format and contain no patient personal information.

10.1.2. Human Review of Unstructured Data (Outcome Validation via Adjudication)

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 at Optum in encrypted electronic form and will be password protected to ensure that only authorized study staff have access. Optum 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, Optum 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. Optum will maintain the ability to link to a list of research-eligible patients identified for medical record retrieval, with the patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws. There is no planned transfer of study data under this study protocol.

10.1.3. Primary Data Collection Without Sites and Investigators (Survey Component)

Optum will use survey vendor ANA Research to complete the survey component of this study. 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 at ANA Research in encrypted electronic and paper forms and will be password protected or secured in a locked room to ensure that only authorized study staff have access. ANA Research 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, ANA Research 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. ANA Research will maintain a confidential list of patients who participated in the study, linking each patient's numerical code to his or her actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the ANA Research study agreement and applicable privacy laws.

10.2. Patient Consent

10.2.1. Structured Data Analysis (Main Analysis; Optum Research Database)

As this study's main analysis involves de-identified structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.2.2. Human Review of Unstructured Data (Outcome Validation via Adjudication)

As the validation of the MCM outcome does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.2.3. Primary Data Collection Without Sites and Investigators (Survey Component)

A 1-page, single-sided informed consent statement will be included in the survey packet and completion of the survey will serve as consent.

10.3. Patient Withdrawal

10.3.1. Structured Data Analysis (Main Analysis; Optum Research Database)

Not applicable

10.3.2. Human Review of Unstructured Data (Outcome Validation via Adjudication)

Not applicable

10.3.3. Primary Data Collection Without Sites and Investigators (Survey Component)

If patient requests withdrawal from study after survey completion, patient will be withdrawn from study.

10.4. Institutional Review Board/Independent Ethics Committee (IEC)

It is the responsibility of RTI-HS and Optum 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/IEC. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

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

10.4.1. RTI International

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

10.4.2. Optum

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

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

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

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

10.4.3. Application for Approval of Medical Record Abstraction

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

- Protocol
- Medical record procurement lists and abstraction form

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

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* (ISPE, 2015), and the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2023). The *ENCePP Checklist for Study Protocols* (ENCePP, 2018) has been completed (see Annex 2).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

11.1. Structured Data Analysis (Main Analysis; Optum Research Database)

This study's main analysis involves data that exist as structured data by the time of study start. It is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an AE (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Human Review of Unstructured Data (Outcome Validation via Adjudication)

In order to conduct validation of the malformation outcomes MCMs, this study protocol requires human review of patient-level unstructured data. Unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer is obligated to report AEs **with explicit attribution** to rimegepant or any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). **Explicit attribution is not inferred by a temporal**

relationship between drug administration and an AE but must be based on a definite statement of causality by a health care provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

1. All serious and non-serious AEs with explicit attribution to rimegepant or **any Pfizer drug** that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 1 business day/3 calendar days[8] of awareness, to Pfizer Safety using the NIS AEM Report Form.
2. Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 1 business day/3 calendar days[8] of awareness, to Pfizer Safety using the NIS AEM Report Form.
3. For exposure during pregnancy in studies of pregnant women, data on the exposure to rimegepant during pregnancy, are not reportable unless associated with serious or non-serious AEs.
4. For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

All the demographic fields on the NIS AEM Report Form may not necessarily be completed, as the form designates, since not all elements will be available due to privacy concerns with the use of secondary data sources. While not all demographic fields will be completed, at the very least, at least 1 patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered a valid one in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "A 35-year-old female…" or "An elderly male…" Other identifiers will have been removed.

Additionally, the onset/start dates and stop dates for "Illness," "Study Drug," and "Drug Name" may be documented in month/year (mmm/yyyy) format rather than identifying the actual date of occurrence within the month /year of occurrence in the day/month/year (DD/MMM/YYYY) format.

All research staff members must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) Training for Vendors with Supplemental Topics*."

These trainings must be completed by research staff members before the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training statements must be provided to Pfizer. Re-training must be completed on an annual basis using the most current YRR with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year,

[8] 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.

the vendor shall ensure that all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

11.3. Primary Data Collection Without Sites and Investigators (Survey Component)

To validate the exposure algorithm, a survey will be administered to women of childbearing age in the Optum database. This survey component does not involve data collection on individual patients by their treating health care professionals and the survey used in this study does not intend to identify product safety information. However, the survey will be completed by participants and a participant could volunteer product safety information. Any safety information for an individual patient that is volunteered by a study participant (e.g., the patient him/herself, health care professional, lay person) during the course of this research must be reported as described below.

The following safety events must be reported on the NIS AEM Report Form: serious and non-serious AEs when associated with the use of the Pfizer product, and scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure **(all reportable, regardless of whether associated with an AE)**, when associated with the use of a Pfizer product.

For exposure during pregnancy in studies of pregnant women, data on the exposure to rimegepant during pregnancy, are not reportable unless associated with serious or non-serious AEs.

In the event that a study participant volunteers product safety information, Optum must complete the NIS AEM Report Form and submit to Pfizer within 1 business day/3 calendar days[9] of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information; complete contact information should be obtained so that, once the NIS AEM Report Form is sent to Pfizer, the NIS AEM Report Form can be assessed and processed according to Pfizer's SOPs, including requests for follow-up to the study participant.

Optum staff who will serve to be available to study participants to answer questions during study participant completion of the survey, review the survey for the study, and address any query from participants about the study must complete the following Pfizer training requirements:

- *"Your Reporting Responsibilities (YRR) with Supplemental Topics."*

These trainings must be completed by study staff prior the start of data collection. All trainings include a "Confirmation of Training Statement" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. The study vendor will also provide copies of all signed training statements to Pfizer. Re-training must be completed on an annual basis using the most current YRR with Supplemental Topics training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, the vendor shall ensure that all vendor personnel complete the updated safety training within sixty (60) calendar days of issuance by Pfizer.

[9] 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.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

In its Guidelines for Good Pharmacoepidemiology Practices, ISPE contends that "there is an ethical obligation to disseminate findings of potential scientific or public health importance" (ISPE, 2015), e.g., results pertaining to the safety of a marketed medication. Study results may be published following guidelines, including those for authorship, established by the International Committee of Medical Journal Editors (ICMJE, 2023). When reporting results of this study, the appropriate Strengthening the Reporting of Observational Studies in Epidemiology checklist will be followed. Communication via appropriate scientific venues will be planned. The marketing authorization holder and the investigator will agree upon a publication policy.

In the event of any prohibition or restriction imposed (e.g., 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 which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

12.1.1. Primary Data Collection Without Sites and Investigators (Survey Component)

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

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14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Doc.Ref. EMA/540136/2009

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

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

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

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[10]	☒	☐	☐	6
1.1.2 End of data collection[11]	☒	☐	☐	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

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

[11] Date from which the analytical data set is completely available.

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section number**
2.1	Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7.5
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	9.2.1
	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
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9, 9.7.5
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))	☒	☐	☐	9.7.5
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?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	9.2.1
	4.2.2 Age and sex	☒	☐	☐	9.2.1
	4.2.3 Country of origin	☒	☐	☐	9.2.1
	4.2.4 Disease/indication	☒	☐	☐	9.2.1
	4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
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

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.1
5.3	Is exposure categorized according to time windows?	☒	☐	☐	9.3.1
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☒	☐	
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.3.1, 9.7.1

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9, 9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.2, 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
7.2	Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.7.3
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	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)	☐	☒	☐	

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)	☒	☐	☐	9.3.1, 9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2, 9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.3, 9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, comedications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.1
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.2
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.3.3
9.4	Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan		**Yes**	**No**	**N/A**	**Section number**
10.1	Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4	Are stratified analyses included?	☒	☐	☐	0
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.3
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.3
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.4
10.8	Are relevant sensitivity analyses described?	☒	☐	☐	9.7.7

Comments:

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

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	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).	☒	☐	☐	9.9
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)	☒	☐	☐	9.9

Comments:

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

Date: 21 August 2023

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Table 12: Medications for the Treatment of Migraine

Medication category	Drugs[a]		Acute migraine treatment/ preventive treatment	Comments
CGRP receptor antagonists	Rimegepant		Acute and preventive treatment	Use of this medication is an inclusion criterion for the rimegepant-exposed group.
	Ubrogepant		Acute treatment	Use of this medication is an exclusion criterion.
	Atogepant		Preventive treatment	Use of this medication is an exclusion criterion.
	Zavegepant		Acute treatment	Use of this medication is an exclusion criterion.
NSAIDs	Celecoxib Diclofenac Diflunisal Etodolac Fenoprofen Flurbiprofen Ibuprofen Indomethacin Ketoprofen Ketorolac	Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin Valdecoxib	Acute treatment	Use of these medications is an inclusion criterion. Includes parenteral forms and solid oral forms (tablets, pills; not liquid forms that are expected to be pediatric preparations) Over-the-counter medications will not be identified (study limitation). NSAIDs will be designated as migraine medication if the woman does not have diagnosis codes for pain conditions (musculoskeletal pain, osteoarthritis, rheumatoid arthritis, other pain conditions) as defined in Section 9.3.3 ascertained using all available data before and including LMP and through the end of pregnancy. Source of medication list: FDA (2018), Wood et al. (2021)
ASA	Acetyl salicylic acid (ASA)		Acute treatment	Low-dose ASA, used for cardiovascular prevention, will not be included. Over-the-counter medications will not be identified (study limitation).

Medication category	Drugs[a]		Acute migraine treatment/ preventive treatment	Comments
Acetaminophen	Acetaminophen		Acute treatment	Use of this medication is an inclusion criterion. Over-the-counter medications will not be identified (study limitation).
Triptans	Almotriptan Eletriptan Frovatriptan Naratriptan	Rizatriptan Sumatriptan Zolmitriptan	Acute treatment	Use of these medications is an inclusion criterion.
Ditans	Lasmiditan		Acute treatment	Use of this medication is an exclusion criterion.
Ergots	Dihydroergotamine Ergotamine		Acute treatment	Use of these medications is an inclusion criterion.
Opioids	Buprenorphine Butorphanol Codeine Fentanyl Hydrocodone Dihydrocodeine Dihydrocodeinone Hydromorphone Levorphanol Meperidine	Methadone Morphine Nalbuphine Oxycodone Oxymorphone Pentazocine Propoxyphene Tapentadol Tramadol	Acute treatment	Use of these medications is an inclusion criterion. Include all parenteral and oral forms. Over-the-counter medications will not be identified (study limitation) Sources: NIDA (2020); Wood et al. (2021)
Beta-blockers	Atenolol Bisoprolol Carvedilol Esmolol Labetalol	Metoprolol Nadolol Pindolol Propranolol Timolol	Preventive treatment	Use of these medications is an inclusion criterion. Do not include ophthalmic forms. Beta-blockers will be designated as migraine medication if the woman does not have diagnosis codes for hypertension as defined in Section 9.3.3, ascertained using all available data before and including LMP and through the end of pregnancy, or if the woman has gestational hypertension, using all available data before and including LMP and through the end of pregnancy.

Medication category	Drugs[a]		Acute migraine treatment/ preventive treatment	Comments
Anti-epileptics	Clonazepam Carbamazepine Divalproex Gabapentin Levetiracetam Lorazepam	Sodium valproate Topiramate Valproate Valproic acid Valproate semisodium	Preventive treatment	Use of these medications is an inclusion criterion. Anti-epileptics will be designated as migraine medication if the woman does not have diagnosis codes for epilepsy as defined in Section 9.3.3, ascertained using all available data before and including LMP and through the end of pregnancy.
Antidepressants	Amitriptyline Bupropion Citalopram Duloxetine Fluoxetine Nefazodone	Nortriptyline Paroxetine Sertraline Trazodone Venlafaxine	Preventive treatment	Use of these medications is an inclusion criterion. Antidepressants will be designated as migraine medication if the woman does not have diagnosis codes for depression, bipolar disorders, anxiety or panic disorders, or obsessive-compulsive disorder as defined in Section 9.3.3, ascertained using all available data before and including LMP and through the end of pregnancy.
Botulinum toxin	Onabotulinumtoxin A		Preventive treatment	Use of this medication is an inclusion criterion. CPT code 64615 is specific for chronic migraine. Because use is generally topical, use for some FDA-approved indications is not of interest for this study: overactive bladder, urinary incontinence, detrusor overactivity, spasticity, cervical dystonia, axillary hyperhidrosis, blepharospasm or strabismus (BOTOX PI, 2021).
CGRP monoclonal antibodies	Eptinezumab Erenumab	Fremanezumab Galcanezumab	Preventive treatment	Use of these medications is an exclusion criterion.

Medication category	Drugs[a]		Acute migraine treatment/ preventive treatment	Comments
Antinauseants	Meclizine Ondansetron Granisetron	Palonosetron Rolapitant Tolazamide		Use of these medications is not included as study medication.
Antipsychotics	Risperidone Paliperidone Aripiprazole	Quetiapine Haloperidol Olanzapine		Use of these medications is not included as study medication.
Steroid	Corticosteroids			Use of these medications is not included as study medication.
Antihistamines	Cyproheptadine			Use of these medications is not included as study medication.

ASA = acetyl salicylic acid; CGRP = calcitonin gene–related peptide; FDA = Food and Drug Administration; LMP = first day of the last menstrual period; NSAID = nonsteroidal anti-inflammatory drug.
Note: The list of medications will be updated as new medications are approved over the course of the study. Updates will be made before each annual interim analysis.
a. Include fixed-dose combinations of drugs available.

Table 13: List of Teratogenic Medications

Drug class/generic name	Half-life	Relevant exposure window
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	Not in TERIS. Assumed window: first, second, and third trimesters
Oxandrolone	13.3 h	Not in TERIS. Assumed window: first, second, and third trimesters
Prasterone	12 h	Not in TERIS. Assumed window: first, second, and third trimesters
Fluoxymesterone	9.2 h	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
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

Drug class/generic name	Half-life	Relevant exposure window
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	Trimethadione—11 to 16 h Paramethadione—12 to 24 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
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	Not in TERIS. 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

Drug class/generic name	Half-life	Relevant exposure window
Cytarabine	1 to 3 h	6 months before conception and first, second, and third trimesters
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
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

Drug class/generic name	Half-life	Relevant exposure window
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
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

Drug class/generic name	Half-life	Relevant exposure window
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 month 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
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

Drug class/generic name	Half-life	Relevant exposure window
Azathioprine	5 h	Primarily first trimester, but other outcomes have been associated with exposures "during pregnancy"
Leflunomide	432 to 456 h	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
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
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 et al. (2016); TERIS (2021); DrugBank online, available at https://go.drugbank.com; product labels, available at: https://www.accessdata.fda.gov/scripts/cder/daf/; summary of product characteristics, available at https://www.ema.europa.eu/en/medicines and https://products.mhra.gov.uk/; and product monographs, available at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html).

Table 14: Characteristics of Women and Pregnancies

Demographic and general characteristics	Time window of ascertainment	Definition	Operational form
Age	On LMP	[Date of LMP – woman's date of birth]/365.25	Continuous variable in years Categorical variable: < 18 years, 18-34 years, ≥ 35 years
Race and ethnicity	On LMP	Imputed variable using an algorithm/model based on mother's given name, last name, and place of residence (census ZIP code [ZIP+4 digits])	• Asian • Black • Hispanic • White • Other and unknown
Duration of health plan enrollment	On LMP	[Date of LMP – woman's date of health plan enrollment]/365.25	Continuous variable in years Categorical variable: < 1 year, 1-2 years, 3-4 years, ≥ 5 years
Year of pregnancy start	On LMP	Calendar year of LMP for current pregnancy	Year
Year of pregnancy end	On date of pregnancy end	Calendar year of end of current pregnancy	Year
Geographic region	On LMP	US region of residence	• Northeast • West • Midwest • South • Unknown
Prior history of medical conditions			
Depression and bipolar disorders	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent
Anxiety and panic disorders	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent
Obsessive-compulsive disorder	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent
Schizophrenia	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent
Epilepsy	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications[a]	Present/absent
Seizures	All available data within 6 months before and including LMP and during pregnancy	Defined through diagnosis codes and applicable medications[b]	Present/absent
Alcohol misuse	Available data within 6 months before and including LMP and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy

Demographic and general characteristics	Time window of ascertainment	Definition	Operational form
Drug misuse	Available data within 6 months before and including LMP and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy
Hyperlipidemia	All available data within 6 months before and including LMP	Defined through diagnosis codes and applicable medications	Present/absent
Diabetes	All available data within 6 months before and including LMP	Defined through diagnosis codes not including gestational diabetes	Present/absent
Hypertension	All available data within 6 months before and including LMP	Defined through diagnosis codes, not including gestational hypertension	Present/absent
Malignancy	All available data before and including LMP	Defined through diagnosis codes	Present/absent
Thyroid disease	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Respiratory disease incl. asthma	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Liver disease	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Chronic kidney disease	All available data within 6 months before and including LMP	Defined through diagnosis codes and procedures	Present/absent
Obesity	All available data within 6 months before and including LMP	Defined through diagnosis codes and proxies (applicable medications and procedures)	Present/absent
Smoking	Available data within 6 months before and including LMP and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy
Cardiovascular diseases	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Pain conditions[c]	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent
Cluster headache	All available data within 6 months before and including LMP	Defined through diagnosis codes	Present/absent

Demographic and general characteristics	Time window of ascertainment	Definition	Operational form
Migraine type	All available data before and including LMP and during pregnancy	Defined through diagnosis codes and applicable medications (see Section 9.2.1.2)	Present/absent If migraine present, type of migraine categories: With aura, intractable With aura, not intractable Without aura, intractable Without aura, not intractable Other
Prior obstetric history			
Gravidity	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Number of pregnancies (0, 1, 2 or more)
Parity	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Number of deliveries or C-sections (0, 1, 2 or more)
Spontaneous abortions	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Present/absent
Spontaneous abortions	All available data within 6 months before current pregnancy	Number of pregnancies ending in spontaneous abortion defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Number of pregnancies (0, 1, 2 or more)
Elective termination	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Present/absent
Preterm births	All available data within 3 years before current pregnancy	Defined using Algorithm A, through diagnosis codes as described in Table 6	Present/absent
Live births with MCM	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm) and through diagnosis codes in linked infants	Present/absent

Demographic and general characteristics	Time window of ascertainment	Definition	Operational form
Stillbirth	All available data within 3 years before current pregnancy	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Present/absent
SGA	All available data within 3 years before current pregnancy	Defined through diagnosis codes	Present/absent
Gestational diabetes	All available data within 3 years before current pregnancy	Defined through diagnosis codes	Present/absent
Gestational hypertension	All available data within 3 years before current pregnancy	Defined through diagnosis codes	Present/absent
Health care utilization			
Number of office visits	Available data within 6 months before LMP	Count of office visits	Number (0, 1, 2, ≥ 3)
Number of telemedicine encounters	Available data within 6 months before LMP	Count of telemedicine encounters	Number (0, 1, 2, ≥ 3)
Number of ED visits	Available data within 6 months before LMP	Count of ED visits	Number (0, 1, 2, ≥ 3)
Number of hospitalizations	Available data within 6 months before LMP	Count of hospitalizations	Number (0, 1, 2, ≥ 3)
Characteristics of current pregnancy			
Multiple pregnancy	During pregnancy	Defined through diagnosis codes	Present/absent
Gestational diabetes	During pregnancy	Defined through diagnosis codes	Present/absent
Gestational hypertension	During pregnancy	Defined through diagnosis codes	Present/absent
TORCH infections	During pregnancy	Defined through diagnosis codes	Present/absent
SARS-COV-2 infection	During pregnancy	Defined through diagnosis codes	Present/absent
Comedications			
Teratogens (see medications listed in Table 13)	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, first trimester of pregnancy, or as indicated by relevant risk window
Cannabinoids	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Preventive cluster headache drugs	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Acute cluster headache drugs	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy

Demographic and general characteristics	Time window of ascertainment	Definition	Operational form
Antidepressants	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antipsychotics	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Oral antidiabetics	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Insulin	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antihypertensive medications	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Lipid-lowering drugs	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antithyroid medications	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Antiplatelet agents	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Anticoagulants	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Anti-emetics and antinauseants	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy
Use of acute migraine medications (see medications listed in Table 12): triptans, ergotamine derivatives, NSAIDs, acetaminophen, and opioids	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, and by trimester of pregnancy Number of users of each medication, number of different medications, number of dispensings, time (days) between dispensings
Use of preventive migraine drugs (medications listed in Table 12): topiramate, anti-epileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitor, and botulinum toxin	Available data within 6 months before LMP and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, and by trimester of pregnancy Number of users of each medication, number of different medications, number of dispensings, time (days) between dispensings

CMV = cytomegalovirus; ED = emergency department; LMP = first day of last menstrual period; MCM = major congenital malformation; NSAID = nonsteroidal anti-inflammatory drug; SARS-COV-2 = severe acute respiratory

syndrome coronavirus 2; SGA = small for gestational age; TORCH infections = toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), herpes simplex, and Zika virus disease; US = United States.

a. Epilepsy will be identified based on at least 2 claims with diagnosis codes of epilepsy or status epilepticus on separate days and 1 or more dispensing for an anti-epileptic drug. Validation studies of various algorithms have shown that the combination of diagnosis codes and claims for dispensing prescriptions for anti-epileptic drugs have the highest positive predictive value (Moura et al., 2017).

b. Isolated diagnosis codes for convulsions or epilepsy, or codes for convulsions or epilepsy that occur (1) only concurrently with codes for drug misuse or with pre-eclampsia/hypertension codes, (2) only around delivery, or (3) concurrent with other comorbidities that could lead to seizures will be defined as seizures (MacDonald et al., 2018).

c. Pain conditions include neuralgias, rheumatoid arthritis, arthritis, osteoarthritis, arthropathies, gout, cervical disc disorders, and dorsalgia.

ANNEX 4. SURVEY ON MIGRAINE MEDICATION USE

To validate the claims-based rimegepant and comparator exposure assessment method, a patient survey will be administered to a subset of women of childbearing age with migraine who are identified from the ORD. More details about the methods of this survey will be documented before survey initiation.

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