NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Prospective, Registry-Based Observational Cohort Study of Zavegepant Safety in Pregnancy
Protocol number	C5301026
Protocol version identifier	Version 3.0
Date	03 September 2024
European Union Post Authorisation Study (EU PAS) register number	Study not registered
Active substance	Zavegepant
Medicinal product	ZAVZPRET™
Research question and objectives	**Research question:** Is there an increased risk of adverse maternal and/or infant outcomes in individuals with migraine exposed to zavegepant during pregnancy? **Primary objectives:** 1. To estimate the prevalence of major congenital malformation (MCM) births (primary outcome) among pregnant individuals with migraine who are (1) exposed to zavegepant (internal exposed cohort), and (2) unexposed to zavegepant (internal comparator cohort). 2. To estimate the relative risk (RR) of MCM births in the exposed internal cohort versus the unexposed internal cohort. **Secondary objectives:** 1. To estimate the prevalence of MCM births in a third cohort of pregnant individuals without migraine (external nonmigraine cohort). 2. To estimate the prevalence of the following secondary outcomes in the 2 internal cohorts: spontaneous abortion (SAB), elective termination, pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia), stillbirth, preterm birth, small-for-gestational-age (SGA) birth, minor congenital malformation birth, infant postnatal growth deficiency, and infant developmental delay.

	3. To estimate the prevalence of the following secondary outcomes in the external nonmigraine cohort: gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia, SAB, elective termination, stillbirth, preterm birth, and SGA birth. 4. To estimate the RR of each of the secondary outcomes in the exposed versus unexposed internal cohorts, if sample size permits.
Country of study	US
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1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACOG	American College of Obstetricians and Gynecologists
AE	adverse event
AEM	adverse event monitoring
ara-G	arabinosyl guanine
ART	assisted reproductive technology
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CGRP	calcitonin gene-related peptide
CI	confidence interval
CPT	current procedural terminology
DAPI	dynamic assessment of pregnancies and infants
DCT	data collection tool
DOC	date of conception
EDC	electronic data capture
EDD	estimated date of delivery
EDP	exposure to a drug during pregnancy
EMA	European Medicines Agency
EU PAS Register	European Union electronic register of Post-Authorisation Studies
EUROCAT	European Surveillance of Congenital Anomalies
FDA	Food and Drug Administration
FSFV	first subject first visit
HCP	healthcare provider
HCPCS	healthcare common procedure coding system
ICD	International Classification of Diseases
IEC	Independent Ethics Committee
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century
IPTW	inverse probability of treatment weighting
IRB	Institutional Review Board
IV	Intravenous
LMP	first day of last menstrual period
LSLV	last subject last visit

Abbreviation	Definition
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	major congenital malformation
NA	not applicable
NIS	non-interventional study
NVSS	national vital statistics system
ORD	Optum Research Database
PASS	post-authorization safety study
PMR	post-marketing requirement
RR	relative risk
SAB	spontaneous abortion
SAP	Statistical analysis plan
SGA	small-for-gestational-age
TERIS	Teratogen Information System
US	United States
VRCC	virtual registry coordinating center
WHO	World Health Organization
YRR	your reporting responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: Prospective, Registry-based Observational Cohort Study of Zavegepant Safety in Pregnancy

Version 3.0, 03 September 2024

Authors: Monica Bertoia, MPH, PhD, Pfizer Inc.; Ronna L. Chan, PhD, MPH, PPD, part of Thermo Fisher Scientific

Rationale and background: Zavegepant (ZAVZPRET™) is a calcitonin gene-related peptide (CGRP) receptor antagonist nasal spray. In March 2023, the United States (US) Food and Drug Administration (FDA) approved zavegepant for the acute treatment of migraine with or without aura in adults. This study will fulfill an FDA post-marketing requirement (PMR) to assess the safety of zavegepant in pregnant individuals.

Research question and objectives:

Research question: Is there an increased risk of adverse maternal and/or infant outcomes in individuals with migraine exposed to zavegepant during pregnancy?

Primary objectives:

1. To estimate the prevalence of MCM births (primary outcome) among pregnant individuals with migraine who are (1) exposed to zavegepant (internal exposed cohort), and (2) unexposed to zavegepant (internal comparator cohort).

2. To estimate the RR of MCM births in the exposed internal cohort versus the unexposed internal cohort.

Secondary objectives:

1. To estimate the prevalence of MCM births in a third cohort of pregnant individuals without migraine (external nonmigraine cohort).

2. To estimate the prevalence of the following secondary outcomes in the 2 internal cohorts: SAB, elective termination, pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia), stillbirth, preterm birth, SGA birth, minor congenital malformation birth, infant postnatal growth deficiency, and infant developmental delay.

3. To estimate the prevalence of the following secondary outcomes in the external nonmigraine cohort: gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia, SAB, elective termination, stillbirth, preterm birth, and SGA birth.

4. To estimate the RR of each of the secondary outcomes in the exposed versus unexposed internal cohorts, if sample size permits.

Study design: Prospective, registry-based observational cohort study. This study will be a new, product-based pregnancy registry.

Population: Three cohorts of pregnant individuals aged 15 to 50 years in the US. Two internal study cohorts will include individuals with migraine exposed to zavegepant during pregnancy and individuals with migraine unexposed to zavegepant during pregnancy who are enrolled in the registry. A third external cohort of pregnant individuals without migraine will be identified from a US health insurance claims database.

Variables: Exposures to zavegepant, other migraine treatments, and other medications/substances during pregnancy; migraine status, pregnancy information, study outcomes (MCM, SAB, elective termination, pregnancy complications [gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia], stillbirth, preterm birth, SGA, minor congenital malformation, infant postnatal growth deficiency, and infant developmental delay), and covariates (including demographics, risk factors for the study outcomes, comorbidities, concomitant medications, and predictors of migraine treatment).

Data sources: For the 2 internal cohorts, information on all study variables will be collected from enrolled pregnant individuals and the healthcare providers (HCPs) involved in their care or the care of their infants. For the external nonmigraine cohort, information on all study variables will be derived from a health insurance claims database (the Optum Research Database (ORD)).

Study size: The registry will aim to enroll 728 pregnant individuals, 364 in each internal cohort. This sample size will be considered sufficient to achieve its primary objectives.

Data analysis: Participant characteristics will be summarized with descriptive statistics for each cohort. The prevalence of each outcome (primary and secondary) will be calculated in the 3 study cohorts by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge. Comparative analyses will be conducted for each outcome using the 2 internal cohorts. Supplementary analyses will be conducted that include pregnant individuals who were excluded from the analysis population (retrospectively enrolled or exposed to teratogens, investigational medications, or non-zavegepant CGRP medications during pregnancy). If sample size permits, subgroup and sensitivity analyses will be performed to examine the extent to which changes in certain methods or assumptions affect the results.

Milestones: Enrollment of individuals in the registry is expected to begin in October 2024, and data collection will continue through June 2037 (unless target enrollment is achieved earlier). Annual interim reports will be submitted to the FDA every June, from 2025 to 2036, and a final study report will be submitted in June 2038. Each annual interim report will include the registry design, methodology, and results to date, including the number of enrolled participants, their characteristics, and their outcomes, by study cohort. The final comprehensive study report will present results from the external nonmigraine cohort, the results of the full statistical analysis, and an interpretive discussion of the results.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
V3.0	03 September 2024	Substantial	4, 8	Revised comparative MCM analysis to a primary (rather than secondary) objective	FDA 08 August 2024 comments
V3.0	03 September 2024	Substantial	9.5	Study size text revised to align with new classification of the MCM comparative analysis as a primary objective	FDA 08 August 2024 comments
V3.0	03 September 2024	Substantial	9.7.4.1	Clarified that propensity score models will only include covariate information from prior to pregnancy start	FDA 08 August 2024 comments
V2.0	23 April 2024	Substantial	8	Added a hypothesis statement for the comparative analyses	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.1	Revised to state that the geographic reach of the registry may be expanded based on study enrollment and approval of zavegepant in countries outside of the US	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.2.1	Inclusion criteria expanded from 18-50 years to 15-50 years	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.3.3	Exposure definition revised to at least one dose taken 5 times the half-life prior to conception for all migraine treatments	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.3.4	Added the pregnancy complications gestational diabetes and gestational hypertension to the list of secondary outcomes	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.3.4	Clarified that all outcome data is collected via HCPs.	Clarification
V2.0	23 April 2024	Substantial	9.3.4, Table 1	Noted that birth defect evaluators will provide a 6-digit defect code, preferred term, and organ system classification	Clarification
V2.0	23 April 2024	Substantial	9.3.5, Table 9	Revised to include the collection of information on maternal psychiatric and substance abuse history, the collection of information on race and ethnicity in a manner consistent with newly published draft FDA guidance, and the collection of information on use of prenatal vitamins and folic acid at baseline and throughout pregnancy	FDA 01 March 2024 comments

Version Identifier	Date	Amendment Type	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
V2.0	23 April 2024	Substantial	9.5.1	Added a feasibility assessment to the Year 4 (2028) interim report to discuss the likelihood of meeting enrollment targets within the US and noted that the comparative MCM analysis may be revised from a secondary to a primary objective if the feasibility assessment indicates a high likelihood of meeting enrollment targets	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.5.4, Table 3, Table 4	Updated elective termination reference prevalence from 19 to 21%	Updated literature
V2.0	23 April 2024	Substantial	9.7.1	Analysis population revised to exclude participants exposed to all CGRP medications (CGRP-related monoclonal antibodies in addition to non-zavegepant CGRP antagonists)	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.7.5	Added a subgroup analysis that stratifies the analysis of MCM prevalence by the organ system of the defect	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.7.7	Added a sensitivity analysis restricting the internal cohorts to the subset of individuals with a pre-pregnancy diagnosis of migraine prior to conception	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	9.9	Limitations revised to include a discussion of the potential for exposure and outcome misclassification, the potential for bias introduced by differential loss to follow-up, and the potential for confounding by indication	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	Annex 4, Table 11	Information collected at pregnancy outcome revised to specify that any postmortem findings for non-live pregnancy outcomes (SAB, stillbirth) with MCMs will be collected	FDA 01 March 2024 comments
V2.0	23 April 2024	Substantial	Annex 5, Table 8	Additional medications added to list of known teratogens	FDA 01 March 2024 comments

6. MILESTONES

Milestone	Planned date	Actual date
Draft protocol	30 November 2023	29 November 2023
Final protocol	30 June 2024	17 May 2024
Registration in the EU PAS register	Prior to the start of data collection	
Study launch/start of data collection (FSFV) *After FDA approval of the final protocol and IRB approval*	31 October 2024	
Annual interim report 1	30 June 2025	
Annual interim report 2	30 June 2026	
Annual interim report 3	30 June 2027	
Annual interim report 4	30 June 2028	
Annual interim report 5	30 June 2029	
Annual interim report 6	30 June 2030	
Annual interim report 7	30 June 2031	
Annual interim report 8	30 June 2032	
Annual interim report 9	30 June 2033	
Annual interim report 10	30 June 2034	
Annual interim report 11	30 June 2035	
Annual interim report 12	30 June 2036	
End of enrollment[a]	30 September 2035	
End of data collection (LSLV)[b]	30 June 2037	
Final study report *Must be submitted within 12 months of the end of data collection*	30 June 2038	

EU PAS = European Union electronic register of Post-Authorisation Studies; FDA = Food and Drug Administration; FSFV = first subject first visit; IRB = institutional review board; LSLV = last subject last visit.
a Date the last individual is enrolled in the study.
b Date the last data point is collected for the study (eg, for the 12-month infant assessment).

7. RATIONALE AND BACKGROUND

In March 2023, the US FDA approved zavegepant (ZAVZPRET™) for the acute treatment of migraine with or without aura in adults. Zavegepant is the first CGRP receptor antagonist available to patients in nasal spray form. CGRP receptor antagonists represent the newest class of migraine treatments that reduce pain through interfering with CGRP-induced vasodilation and inflammation (Edvinsson et al. 2018).

Migraine is common, especially among women, with a prevalence of 21% in US women and 10% in US men (Burch et al. 2018). Prevalence peaks in mid-life and women of reproductive age carry the greatest migraine burden (Croop et al. 2019). Migraine is associated with a higher risk of some adverse pregnancy outcomes including pre-eclampsia and gestational hypertension (Aukes et al. 2019).

While no adverse developmental effects were observed in zavegepant animal studies, there are limited data on the safety of zavegepant use in pregnant individuals (ZAVZPRET™ label 2023). This study will address this gap in information on the safety of zavegepant when used in pregnancy in terms of risk of maternal and/or infant outcomes. This will be a new, product-based registry that recruits pregnant women with migraine as well as pregnant women taking zavegepant. This non-interventional study (NIS) is designated as a post-authorization safety study (PASS) and is a post-marketing commitment to the FDA.

8. RESEARCH QUESTION AND OBJECTIVES

Research question: Is there an increased risk of adverse maternal and/or infant outcomes in individuals with migraine exposed to zavegepant during pregnancy?

Primary objectives:

1. To estimate the prevalence of MCM births (primary outcome) among pregnant individuals with migraine who are (1) exposed to zavegepant (internal exposed cohort), and (2) unexposed to zavegepant (internal comparator cohort).

2. To estimate the RR of MCM births in the exposed internal cohort versus the unexposed internal cohort.

   Hypothesis: There is no difference in the risk of MCM births between zavegepant-exposed and zavegepant-unexposed participants (ie, the null hypothesis or RR of 1.0).

Secondary objectives:

1. To estimate the prevalence of MCM births in a third cohort of pregnant individuals without migraine (external nonmigraine cohort).

2. To estimate the prevalence of the following secondary outcomes in the 2 internal cohorts: SAB, elective termination, pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia), stillbirth, preterm birth, SGA birth, minor congenital malformation birth, infant postnatal growth deficiency, and infant developmental delay.

3. To estimate the prevalence of the following secondary outcomes in the external nonmigraine cohort: gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia, SAB, elective termination, stillbirth, preterm birth, and SGA birth.

4. To estimate the RR of each of the secondary outcomes in the exposed versus unexposed internal cohorts, if sample size permits.

   Hypothesis: There is no difference in the risk of secondary outcomes between zavegepant-exposed and zavegepant-unexposed participants (ie, the null hypothesis or RR of 1.0).

9. RESEARCH METHODS

9.1. Study design

This registry-based, prospective observational cohort study will enroll and follow pregnant individuals 15 to 50 years of age in the US, including individuals with migraine exposed to zavegepant during pregnancy and individuals with migraine unexposed to zavegepant during pregnancy. Based on study enrollment and approval of zavegepant in countries outside of the US, the geographic reach of the registry may be expanded (see Section 9.5.1 for more details). This study will be a new, product-based pregnancy registry. Participation in the registry is voluntary and participants can withdraw their consent to participate at any time. Data will be collected from enrolled pregnant individuals and the HCPs involved in their care or the care of their infants.

An external cohort of pregnant individuals without migraine will provide context to the main study results by estimating background rates of the study outcomes among pregnant individuals. This cohort will be identified within a US-based health insurance claims database. The corresponding set of exposure, outcome, and covariate variables will be derived from the structured claims data, with the exception of MCM, which will be validated by medical records. The external nonmigraine cohort will not assess minor congenital malformations, postnatal growth deficiency, or infant developmental delay as these outcomes are not captured well in claims data.

The primary study outcome is MCM and the secondary outcomes are SAB, elective termination, pregnancy complications (gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia), stillbirth, preterm birth, SGA, minor congenital malformation, postnatal growth deficiency, and infant developmental delay. The main measures of effect are the prevalence of each outcome in the 3 study cohorts (2 internal and 1 external) and the RR of each outcome, comparing the 2 internal cohorts.

This study design aligns with current FDA guidance for designing and implementing pregnancy exposure registries (FDA 2019). All assessments described in this protocol are performed as part of normal clinical practice or standard practice guidelines for the patient population and HCP specialty in the countries where this NIS is being conducted. The schedule of office visits and treatment regimens will be determined by HCPs. Only data that are typically documented in participants' medical records during the course of medical care

will be collected. No additional laboratory tests or HCP assessments will be required for this study.

9.2. Setting

The 2 internal study cohorts will be derived from eligible individuals enrolled in the pregnancy registry. The virtual registry coordinating center (VRCC) will coordinate enrollment and data collection for the internal study cohorts (details provided in Section 9.4). The external nonmigraine cohort will include individuals identified within the claims database. All 3 cohorts of pregnant individuals will be identified in the US during the study period.

9.2.1. Inclusion criteria (internal cohorts)

Individuals must meet all of the following criteria to be eligible for inclusion in the study:

1. 15 to 50 years of age at the time of enrollment
    - Per FDA recommendation, age range expanded to <18 years
2. Currently or recently pregnant (recently pregnant defined as enrollment within 1 year of pregnancy outcome)
    - Only prospectively enrolled participants (ie, individuals who are currently pregnant at enrollment) will be included in the main analysis population; retrospectively enrolled participants (ie, individuals whose pregnancy outcomes have occurred) will be included in supplementary analyses
3. Have a current diagnosis of migraine (confirmed by HCP, see Section 9.3.2)
4. Personally signed and dated informed consent document or, upon waiver of written consent by the relevant IRB/independent ethics committee (IEC), verbal consent, indicating that the individual (or a legally acceptable representative) has been informed of all pertinent aspects of the study
5. Authorization for their HCP(s) to provide data to the registry
6. Contact information (for participant and HCPs)

9.2.2. Exclusion criteria (internal cohorts)

There are no exclusion criteria for this study.

9.2.3. Internal zavegepant-exposed cohort

Eligible individuals will be included in the zavegepant-exposed cohort if they are exposed to zavegepant during pregnancy. Section 9.3.3 describes the definition of exposed.

Individuals exposed to zavegepant and other acute or preventive migraine treatments will be included in the internal exposed cohort. A sensitivity analyses is planned that will restrict the internal exposed cohort to individuals exposed to zavegepant only (Section 9.7.7.3).

9.2.4. Internal comparator cohort

All remaining eligible individuals who are not exposed to zavegepant during pregnancy will be included in the comparator cohort. This cohort will include individuals who are and are not exposed to migraine treatments.

If sample size permits, the main analysis will restrict this cohort to treated individuals only, else this restriction will be applied in a sensitivity analysis (Section 9.7.7.4). A treated comparator cohort is expected to improve comparability of the 2 internal cohorts by selecting groups of individuals with similar migraine severity, a potential risk factor for some of the study outcomes. Individuals who are not treated may have milder disease.

9.2.5. Study period

The registry will launch following FDA and institutional review board (IRB) approval of the protocol. Enrollment is expected to begin in October 2024 and end in September 2035. Data collection will continue through June 2037 (unless target enrollment is achieved earlier). For each enrolled pregnant individual, participation will begin at enrollment and end at pregnancy outcome or 12 months after pregnancy outcome (if live birth).

9.2.6. External nonmigraine cohort

An external cohort of pregnant individuals without migraine will provide context to the main study results by estimating background rates of the study outcomes among pregnant individuals. This cohort will be identified within the ORD, a US-based health insurance claims database. See Section 9.4.5 for details about the ORD. Methods for identifying and characterizing the external nonmigraine cohort are described in detail in Annex 1, the draft protocol "Observational Cohort Study of Zavegepant Safety in Pregnancy Within a US Claims Database."

In brief, all pregnant individuals without migraine during the study period will be identified within the ORD using established methods (Bertoia et al. 2022). Pregnancies, pregnancy periods, and migraine diagnosis will be identified using codes from health insurance claims (eg, International Classification of Diseases [ICD] diagnosis and procedure, Current Procedural Terminology [CPT], Healthcare Common Procedure Coding System [HCPCS]). Pregnancy outcomes and covariates will be identified by codes, except for MCM which will be initially identified by codes and then validated by medical records. Infants will be linked to their mothers using delivery date, birth date, and family insurance number.

Background prevalence estimates will be gathered from the literature for additional context. Published prevalence data for the study outcomes among the general population of pregnant individuals (with and without migraine) will be reviewed and summarized. This literature assessment will include published data on any observed excess risk of the study outcomes associated with migraine itself or migraine severity. The published data may include results from the US (eg, the Metropolitan Atlanta Congenital Defects Program [MACDP], the Centers for Disease Control and Prevention [CDC] National Vital Statistics System [NVSS]) and non-US (eg, European Surveillance of Congenital Anomalies [EUROCAT]) sources.

9.3. Variables

9.3.1. Pregnancy period

The registry will conform to the American College of Obstetricians and Gynecologists (ACOG) recommendations for determining the "best" estimated date of delivery (EDD); then, EDD will be used to calculate gestational age. Per ACOG, gestational age and the EDD should be determined by the obstetric HCP as soon as data are obtained regarding the last menstrual period (LMP), first accurate ultrasound, or both. ACOG considers ultrasound measurement of the embryo or fetus in the first trimester (up to and including $13^{6/7}$ gestational weeks) the most accurate method to establish or confirm gestational age and discourages against changing the EDD based on subsequent ultrasounds. Any pregnancy without an ultrasound before $22^{0/7}$ gestational weeks to confirm or revise the EDD should be considered suboptimally dated. If the pregnancy resulted from assisted reproductive technology (ART), the obstetric HCP should use ART-derived gestational age (eg, based on age of embryo and date of transfer) to determine EDD. ACOG further recommends that the best estimate of EDD by the obstetric HCP, rather than estimates based on LMP alone, be used for research purposes (ACOG 2017).

Based on ACOG's recommendations, the registry will collect the EDD from the obstetric HCP, and the HCP will report whether the EDD was calculated based on LMP, ultrasound, or ART data. If ultrasound-based, whether the ultrasound was performed at $<14^{0/7}$, $14^{0/7}$ to $21^{6/7}$, or $\geq 22^{0/7}$ gestational weeks will also be recorded. EDD data will be collected on each data collection form throughout pregnancy. If the HCP reports a corrected EDD on subsequent forms that is different from the EDD initially reported, the registry will evaluate whether a correction is appropriate, based on the timing of the correction and the methods used to determine the corrected EDD, and follow-up with the HCP, if needed. Based on EDD, the following information will be calculated:

- First day of LMP, defined as $0^{0/7}$ gestational weeks, will be calculated as EDD minus 280 days (40 weeks)
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP
    - Gestational weeks $0^{0/7}$ to $13^{6/7}$ will be considered the first trimester
    - Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester
    - Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester
- Date of conception (DOC), defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks)

If EDD is not reported by the HCP but LMP data are available, the registry will use first day of LMP to calculate EDD, gestational age, and DOC.

9.3.2. Migraine

Individuals must have a confirmed, current diagnosis of migraine with or without aura to be eligible for inclusion in the registry. Some individuals will have been diagnosed before conception and others during pregnancy. Individuals will report whether they have been diagnosed with migraine and HCPs (obstetric or prescriber) will confirm. HCPs and/or participants will provide details regarding migraine severity and date of diagnosis.

It is expected that HCPs will diagnose migraine according to the standard clinical criteria outlined in the International Classification of Headache Disorders, Third Edition (IHS 2018). HCPs will be asked to confirm that the individual was diagnosed with migraine, not to confirm that all clinical criteria were met.

9.3.3. Exposures

Migraine therapy details (prescribed dose, route, frequency, start/end dates, and indication [acute only, preventive only, or acute and preventive]) will be collected from HCPs at enrollment, at the end of the second trimester, and at the pregnancy outcome. Additional migraine therapy (prescription and non-prescription) exposure information will be captured in real-time or near real-time from the participants via an exposure diary/migraine log. See Section 9.4.3 for more information.

For all migraine treatments (acute and preventive), individuals will be considered exposed during pregnancy if ≥1 dose is taken during pregnancy or up to 5 times the product's half-life prior to conception. Annex 3 provides a full list of migraine treatments and their half-lives.

This detailed information will allow for an assessment of temporality between medication exposure and outcome timing. It will also allow exposure to be categorized by trimester (Section 9.3.1) and by the outcome-specific relevant etiologic period (Table 6).

Depending on the timing of zavegepant exposure during pregnancy, some zavegepant-exposed individuals will not contribute to all outcome analyses, as each outcome is associated with an outcome-specific relevant etiologic period (summarized in Table 6). For example, the relevant etiologic period for the primary outcome MCM is the first trimester, whereas the relevant etiologic period for SGA is the full pregnancy period. Hence, pregnant individuals who are exposed to zavegepant after the first trimester will not contribute to the analysis of MCM.

9.3.4. Outcomes

Table 1 presents the definitions of the outcomes of interest. MCM is the primary outcome of interest and all other outcomes are secondary. All outcome data are collected via HCPs. For outcomes not simply reported by the HCP via data collection forms, additional information on outcome ascertainment is provided in Table 1.

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Additional information on ascertainment
Major congenital malformation (MCM)	An abnormality of body structure or function that is present at birth, is of prenatal origin (ie, birth defect), has significant medical, social, or cosmetic consequences for the affected individual, and typically requires medical intervention (CDC 2020)	The registry defines and codes MCMs with criteria specified by the CDC MACDP (CDC 2021). a) Exclusion criteria for analyses: To avoid misattribution of the malformation to the medication, MCMs not associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at <36 gestational weeks (eg, patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (eg, hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses), will not be considered MCMs in the statistical analyses (Holmes and Westgate 2011). b) Adjudication process: A panel of 2 independent experts in clinical genetics and neonatology, blinded to exposure, will review all MCMs reported to the registry and classify them using the CDC's MACDP system. For each defect, coding will result in the evaluators providing a 6-digit defect code, preferred term, and organ system classification. Additionally, the birth defect evaluators will provide their opinions regarding the timing of the development of observed defects. If additional information is needed to aid in classification, the birth defect evaluators will request additional information using the targeted follow-up process outlined in Annex 4. These assessments will be recorded in the database. If there is a discrepancy, a third expert will independently review and code the case serving as tie breaker. These reviews will occur soon after the MCM is reported. Additional reviews will occur if new information is received for the case, as well as the possible temporal association between exposure (to zavegepant) and the development of observed defects. Additionally, the Steering Committee will review all MCM cases reported to the registry and reach consensus on the coding of each case. The Sponsor will not be involved in any activities related to case review or adjudication.
Spontaneous abortion (SAB)	An involuntary fetal loss or the expulsion of the products of conception occurring at <20 gestational weeks	Section 9.3.1 provides information on the methods used to calculate gestational age.
Elective termination	A voluntary fetal loss or interruption of pregnancy that occurs for any reason, including but not limited to for the preservation of maternal health or due to fetal abnormalities	None

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Additional information on ascertainment
Gestational diabetes	Any degree of glucose intolerance with onset or first recognition during pregnancy (ADA 2004)	None
Gestational hypertension	High blood pressure occurring at >20 gestational weeks without signs of liver or kidney damage (eg, proteinuria) (ACOG 2002a)	None
Pre-eclampsia	A disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term, and proteinuria. Or, in the absence of proteinuria, it is defined as new-onset hypertension with the new onset of any of the following: • Thrombocytopenia: platelet count less < 100 ,000/mL • Renal insufficiency: serum creatinine concentrations > 1.1mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease • Impaired liver function: elevated blood concentrations of liver transaminases to twice normal concentration • Pulmonary edema • New-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms (ACOG 2020a)	None

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Additional information on ascertainment
Eclampsia	New-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use (ACOG 2020a)	None
Stillbirth	Involuntary fetal loss occurring at ≥20 gestational weeks or, if gestational age is unknown, a fetus weighing ≥350 g (ACOG 2020b)	Section 9.3.1 provides information on the methods used to calculate gestational age.
Preterm birth	A live birth occurring at <37 gestational weeks (ACOG 2022)	Section 9.3.1 provides information on the methods used to calculate gestational age.
Small for gestational age (SGA)	Birthweight <10th percentile for sex and gestational age using standard growth charts for full and preterm live-born infants (Battaglia and Lubchenco 1967)	For the determination of SGA, the registry will utilize the sex-specific international growth reference standards from the International Fetal and Newborn Growth Consortium for the 21st Century (INTERGROWTH-21st) for those born between $24^{0/7}$ and $42^{6/7}$ gestational weeks (Villar et al, 2014; Villar et al, 2016). The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multiethnic, diverse population, and have been specifically developed for modern research.
Minor congenital malformation	An anomaly or abnormality of body structure that is present at birth, is of prenatal origin (ie, birth defect), poses no significant health problem in the neonatal period, and tends to have limited social or cosmetic consequences for the affected individual (CDC 2020)	The registry defines and codes minor congenital malformations with criteria specified as defined by CDC (CDC 2019). The same process for adjudicating MCMs will be used to adjudicate minor congenital malformations.
Postnatal growth deficiency	Weight, length, or head circumference in <10^{th} percentile for sex and chronological age using standard growth charts	Postnatal growth deficiency, as part of routine care, will be evaluated at 4 and 12 months of infant age; deficiencies in weight, length, and head circumference will be evaluated separately. For the determination of postnatal growth deficiency, the registry will utilize the sex-specific international growth reference standards from the WHO for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age (CDC 2010).

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Additional information on ascertainment
Infant developmental delay	Failure to achieve the developmental milestones for chronological age, as defined by the CDC (CDC 2022)	Infant developmental delay, as part of routine care, will be evaluated at 4 and 12 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development), separately.

ACOG = American College of Obstetricians and Gynecologists; CDC = Centers for Disease Control and Prevention; INTERGROWTH-21st = International Fetal and Newborn Growth Consortium for the 21st Century; MACDP = Metropolitan Atlanta Congenital Defects Program; MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age; US = United States; WHO = World Health Organization.

9.3.5. Covariates

The following variables will be collected (or derived from collected data) by the registry for the internal cohorts:

- Geographic region
- Calendar year at conception
- Maternal age at conception
- Maternal race (White, Hispanic or Latino, Black or African American, Asian, American Indian or Alaska Native, Middle Eastern or North Africa, Native Hawaiian or Pacific Islander)
- Maternal ethnicity
- Marital status
- Maternal insurance status (commercial insurance, Medicaid insurance, or uninsured)
- Proxies for maternal socioeconomic status, including maternal education, employment status, and income
- Maternal pre-pregnancy body mass index, calculated from pre-pregnancy weight and height
- Gestational age at registry enrollment
- Method of conception
- Number of fetuses
- Fetal/infant sex
- Concurrent and past maternal medical conditions, including thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders (eg, substance abuse disorder), hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (eg, congenital uterine abnormalities)
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including gestational diabetes, gestational hypertension, pre-eclampsia, eclampsia, preterm labor, placental abruption, and incompetent cervix
- Prenatal testing (current pregnancy)
- Number of previous pregnancies
- Previous pregnancy outcomes (SAB, stillbirth, elective termination, live birth)
- Previous pregnancy complications
- Characteristics of previous live births (preterm, SGA)
- Previous fetus/infant with congenital malformations (major and minor)
- Family history of congenital malformations (major and minor)

- Characteristics of migraine disease, including date of diagnosis, typical severity immediately prior to pregnancy (ie, to establish baseline severity), migraine frequency (episodic or chronic), presence of aura, presence of medication overuse, headache, and duration (ie, time since diagnosis and age at first diagnosis)
- Maternal exposure to other drugs or biological products, including prescription and non-prescription drugs, dietary supplements (including prenatal vitamins and folic acid), neuromodulation devices, and vaccines, during pregnancy and gestational age at exposure
- Maternal exposure to tobacco, alcohol, marijuana, and recreational or illicit drugs during pregnancy and timing of exposure

Covariate information for the external nonmigraine cohort is provided in Annex 1.

9.4. Data sources

This will be a new, product-based pregnancy registry conducted by PPD (part of Thermo Fisher Scientific). PPD has more than 30 years of experience conducting pregnancy registries and similar studies including more than 50 pregnancy and infant follow-up studies that meet FDA and/or European Medicines Agency (EMA) guidelines for monitoring pregnancy exposures. The ongoing CIBINQ (abrocitinib) and MONITOR (rimegepant) pregnancy registry PASS studies are 2 such examples (PPD 2023).

9.4.1. Enrollment

A multi-modal approach will be used to deliver registry education and recruitment materials to targeted HCPs and patients. Recruitment will include pregnant women with migraine, pregnant women taking zavegepant, and their HCPs (see Annex 2 for details). This approach involves direct-to-HCP outreach as well as online and print advertising directed to HCPs and patients. Recruitment and retention strategy details (eg, website, HCP brochures) are described in Annex 2.

The VRCC will coordinate enrollment and data collection. Pregnant individuals who are interested in participating in the study will answer a set of screening eligibility questions via a web-based/mobile application or by calling the VRCC. If eligible, the individual will be asked to provide informed consent, their primary contact information, alternate contact information, contact information for HCPs who are/will be involved in their care or the care of their infant, and medical releases to allow these HCPs to provide data to the registry.

9.4.2. Data reporters

For the internal cohorts, information on all study variables will be collected from enrolled pregnant individuals and the HCPs involved in their care or the care of their infants. For the external nonmigraine cohort, information on all study variables will be derived from a health insurance claims database (ORD).

As described in Table 2, it is anticipated that most obstetric data will be collected from the participant’s obstetric HCP (eg, obstetrician, family practitioner, general practitioner who

provides care during pregnancy), and that most infant data will be collected from the infant's pediatric HCP (eg, pediatrician, family practitioner, general practitioner who provides pediatric care). After enrollment, the registry may also request data from other HCPs involved in the participant's or infant's care (eg, prescriber, specialist) or from additional HCPs who were not identified at enrollment (eg, if a participant does not know who their pediatric HCP will be at the time of enrollment or switches HCPs after enrollment) after appropriate medical releases are obtained from the participant.

Reporters will use electronic forms or paper data collection forms that can be submitted via e-mail/fax, or via phone interview. HCP reporters will be instructed to transcribe data from the participant's or infant's medical records into the data collection forms.

9.4.3. Data collection schedule

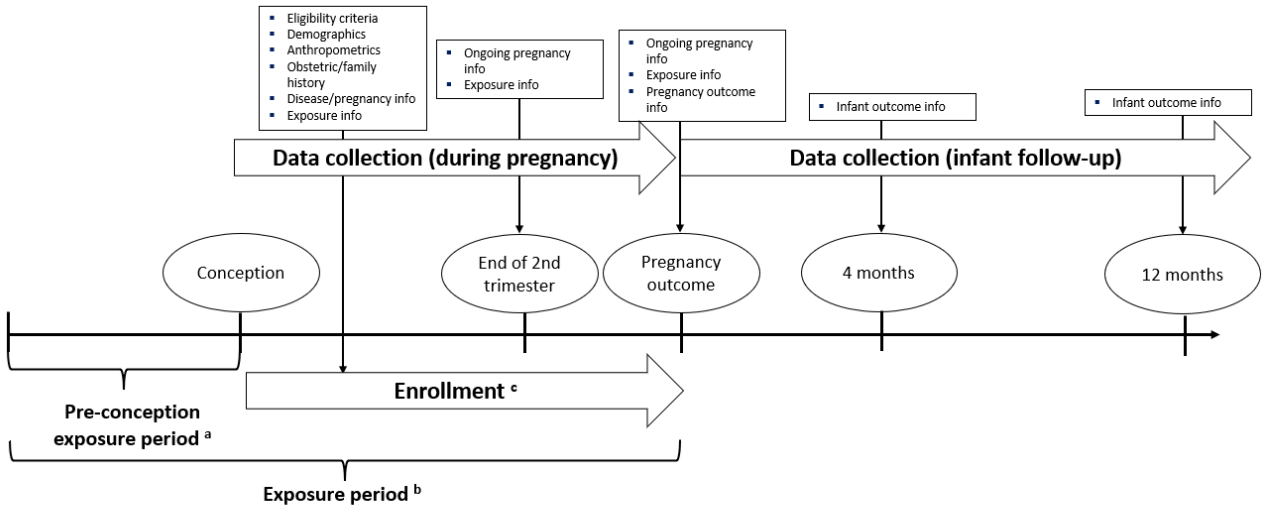
All participants will be followed through the end of pregnancy and all liveborn infants will be followed through 1 year of age (Figure 1). Information will be collected at enrollment, at the end of the second trimester (approximately 26 gestational weeks), and at the end of pregnancy (live birth or fetal loss). Infant data will be collected at 4 and 12 months of age. Most participants are expected to enroll (first data collection timepoint) in the first trimester. The second data collection timepoint is planned for the end of the second trimester, because it is after important diagnostic tests like the 20-week anatomy scan.

Data on migraine headaches and exposures to acute and preventive migraine therapies (prescription and non-prescription) during pregnancy will be collected in real-time or near real-time from participants via patient-completed logs. Most participants will probably choose to complete the exposure log/migraine log via the registry's web-based/mobile application; however, alternate methods for completion will be available, including via telephone and paper data collection form that may be submitted to the registry via fax, e-mail, or hardcopy mail. Weekly reminders to continuously complete the log will be sent to participants by the VRCC via the web-based/mobile application, e-mail, and/or telephone.

9.4.4. Data collection details

Figure 1 and Table 2 provide a summary of the data collection forms and schedule. Additional details are provided in Annex 4, including a summary of information collected at each timepoint (eg, at enrollment, at end of second trimester).

Figure 1. Data Collection Schedule



[a] Time to product elimination (5 times terminal half-life); zavegepant half-life = 6.55 hours; therefore, time to elimination = 2 days
[b] If a participant is exposed to the product during this time period, she will be considered exposed during pregnancy
[c] Participants may be retrospectively enrolled into the registry up to one year after pregnancy outcome but will not be included in main analysis

Table 2. Summary of Data Collection Forms

Data collection form	Reporters	Timing of completion	Data collected
Registration Form for Participants	Participant	Enrollment	• Registration information, including eligibility criteria • Maternal demographic characteristics • Maternal pre-pregnancy anthropometrics • Migraine information
Weekly Log for Migraine Headaches and Acute Medications	Participant	At enrollment, then in real-time or in near real-time, and submitted weekly during pregnancy	• Migraine information • Maternal exposures to acute migraine medications during pregnancy
Monthly Log for Preventive Migraine Medications	Participant	At enrollment, then in real-time or in near real-time, and submitted monthly during pregnancy	• Maternal exposures to preventive migraine medications during pregnancy
Registration Form for HCPs	Obstetric HCP and prescribing HCP, if needed	Enrollment	• Registration information, including eligibility criteria • Maternal obstetrical history • Family history of congenital malformations • Migraine information

Table 2. Summary of Data Collection Forms

Data collection form	Reporters	Timing of completion	Data collected
			• Baseline pregnancy information
Pregnancy Information Form	Obstetric HCP and prescribing HCP, if needed	Enrollment, end of second trimester*, and EDD/pregnancy outcome*	• Ongoing pregnancy information • Maternal exposures during pregnancy
Pregnancy Outcome Form	Obstetric HCP and pediatric HCP, if needed	EDD/pregnancy outcome	• Pregnancy outcome information
Infant Outcomes Form	Pediatric HCP	4 and 12 months after delivery	• Infant outcome information at 2, 4, 6, and 12 months
Targeted Follow-up Form	Obstetric, pediatric, or other HCP	Any time after pregnancy outcome	• Targeted follow-up information

EDD = estimated date of delivery; HCP = healthcare provider.

* Obtain updated information since the previous contact.

9.4.5. External comparator cohort

The patients included in the nonmigraine external comparator cohort 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 patients covered by this health plan are geographically diverse across the US and comprise approximately 3% to 4% of the US population. Published methods are used to identify pregnancies and pregnancy outcomes in the ORD (Bertoia et al. 2022).

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 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 (eg, 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, more than 1 million pregnancies have been identified from 01 October 2015 through 30 September 2020 (Bertoia et al. 2022).

Within DAPI, mother and infant records are 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 to 100,000 pregnancies are identified each year within the ORD. 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. This may occur if the newborn was 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 was covered under their 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 outcome 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

9.5.1. Assessment of study feasibility

To assess the feasibility of this study, data-based assumptions regarding the prevalence of migraine, pregnancy, and zavegepant uptake were made to estimate the number of women who will potentially be exposed to zavegepant during pregnancy. The prevalence of migraine among women of childbearing age was assumed to be 20%, and the proportion receiving pharmacotherapy was assumed to be 50% (Buse 2013). It was further assumed that 1% of those receiving pharmacotherapy would be treated with zavegepant. These assumptions were applied to the population of women of childbearing potential in the US (estimated to be 74,960,628 women aged 15 to 49 years; US Census 2021), which yielded 74,960 women of childbearing potential who will potentially receive zavegepant. After application of the general fertility rate in the US (56.0 births per 1,000 women aged 15 to 44 years; Osterman 2022), it was estimated that 4,198 live births may potentially be exposed to zavegepant in utero. Given the 3% MCM rate among live births (CDC 2008) in the US general population, these 4,198 zavegepant-exposed live births can be expected to result in approximately 126 live births with MCM.

If the registry were to capture one-fourth of the live births exposed to zavegepant in utero, the registry would be expected to capture approximately 31 live births with MCMs.

A feasibility assessment will be included in the 4th annual interim report (2028). This feasibility assessment will discuss the likelihood of meeting enrollment targets within the US. If the likelihood is low, this assessment will discuss the potential for expanding the registry to non-US countries in which zavegepant is marketed.

9.5.2. Target enrollment

The registry will aim to enroll 728 pregnant individuals, 364 in each of the 2 internal cohorts. This sample size will allow the study to achieve its primary objectives (Sections 9.5.3 and 9.5.4). The primary objectives relate to the primary outcome MCM, the outcome with the most restrictive denominators and one of the lowest prevalence estimates in the general population.

The frequency of zavegepant exposure in pregnant individuals and their willingness to enroll in a pregnancy registry is unknown. The annual interim reports will provide information on zavegepant uptake and recruitment of the 2 internal cohorts. Additionally, the 4th annual interim report in 2028 will include a feasibility assessment that discusses the likelihood of meeting enrollment targets within the US. Furthermore, potential expansion of enrollment outside of the US to countries where zavegepant is approved will be considered.

9.5.3. Sample size for descriptive analyses

Sample size calculations were performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC) and PASS 2021 Power Analysis and Sample Size software (version 21.0.3, CSS, LLC, Kaysville, Utah, USA) for the outcomes of interest. For the calculations, general population prevalence estimates were obtained for the outcomes of interest from various sources, including the MACDP, NVSS, the National Institute for Child Health and Human Development's Consecutive Pregnancies Study and Consortium on Safe Labor Study, and published literature.

For the descriptive primary objective (to estimate the prevalence of MCM), a sample size of 200 participants per cohort will yield ±3% precision. For the comparative primary objective (to compare the prevalence of MCM in 2 internal cohorts), a sample size of 364 participants per cohort will be targeted to detect a 3-fold increase in the risk of MCM.

Calculations were performed to determine the achievable precision of outcome prevalence estimates for a range of sample sizes. Table 3 presents the sample size by outcome (number of live births or pregnant women, depending on the outcome) required in each cohort to detect a range of precisions, from 1% to 5%. These sample sizes apply to the 2 internal cohorts as well as the external nonmigraine cohort, assuming a similar population prevalence in all 3 cohorts. Precision is calculated as the half-width of the 2-sided 95% confidence interval (CI) using the Wilson (score) method for binomial proportions. As shown in Table 3, 145 live births in the analysis population of each cohort are needed to estimate the prevalence of MCM with ±3% precision.

To estimate the number of pregnant individuals who will need to be enrolled to result in 145 live births (with first trimester exposure, if in the exposed cohort) in the analysis population per cohort, several factors were considered, including the expected proportion of live births in the registry, the proportion of enrolled individuals with exposure to zavegepant in the first trimester, and the proportion of enrolled individuals expected to be excluded from the analysis population. Reasons for exclusion from the analysis population are provided in Section 9.7.1. It was assumed that 90% of enrolled individuals would be exposed in the first

trimester, 90% of enrolled pregnancies would result in a live birth (Covington et al. 2010; Veley et al. 2020), and 10% of enrolled individuals would be excluded from the analysis population. Given these assumptions, to attain 145 live births per cohort, 200 pregnant individuals would need to be enrolled in each of the 2 cohorts of the study population, and a minimum of 400 individuals would need to be enrolled in the registry. This sample size will enable the study to estimate the prevalence of MCM in each cohort with ±3% precision with 95% confidence.

9.5.4. Sample size for comparative analyses

As shown in Table 4, 265 live births in the analysis population of each cohort are needed to detect an MCM RR of 3. Given the same assumptions applied above, to attain 265 live births (with first trimester exposure, if in the exposed cohort) in the analysis population per cohort, 364 pregnant individuals would need to be enrolled in each of the 2 cohorts of the study population, and a total of 728 individuals would need to be enrolled in the registry. Additionally, Table 5 shows that, without any adjustments for multiple comparisons, the proposed sample size will afford the study >80% power to detect a RR of 3.0 for all other outcomes except eclampsia and stillbirth (for which the study will have 5.9% and 21.4% power, respectively, to detect a RR of 3.0).

Table 3. Precision-based Sample Size Calculations

Outcome	Reference Prevalence	Reference	Denominator (from rate in literature)	Sample Size Needed per Cohort to Estimate Prevalence with Specified Precision								
				1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%
MCM	3.0%	CDC 2008	Live births	1,143	521	303	201	145	111	89	73	61
SAB	11.8%	Wu et al. 2019	Pregnant women	4,000	1,779	1,002	642	446	328	252	199	162
Elective termination	20.6%	Jones et al. 2022	Pregnant women	6,282	2,791	1,569	1,004	697	512	391	309	250
Gestational diabetes	6.9%	Martin et al. 2021	Pregnant women	2,475	1,104	625	402	282	209	161	129	105
Gestational hypertension	6.5%	Butwick et al. 2020	Pregnant women	2,343	1,046	592	382	268	199	154	123	101
Pre-eclampsia	3.8%	Ananth et al. 2013	Pregnant women	1,423	642	369	242	173	131	103	84	70
Eclampsia	0.281%	Butwick et al. 2020	Live births	249	150	107	82	67	56	48	42	37
Stillbirth	0.596%	MacDorman and Gregory 2015	Live births and stillbirths	333	184	124	93	74	61	52	45	39
Preterm birth	8.47%	Martin et al. 2021	Singleton live births	2,983	1,329	750	482	336	248	191	152	124
SGA	10.0%	By definition	Singleton live births	3,461	1,540	868	557	388	286	219	174	141
Postnatal growth deficiency	10.0%	By definition	Singleton live births	3,461	1,540	868	557	388	286	219	174	141
Infant developmental delay	13%	Rosenberg et al, 2008	Live births	4,346	1,932	1,087	696	484	356	273	216	175

CDC = Centers for Disease Control; MCM = major congenital malformation; reference prevalence = prevalence of outcome in general population for pregnant individuals of any age; SAB = spontaneous abortion; SGA = small for gestational age.
Sample size calculations were performed in the PASS software for the outcomes of interest; precision is calculated as the half-width of the 2-sided 95% CI using the Wilson (score) method for binomial proportions.

Table 4. Relative Risk-based Sample Size Calculations

Outcome	Prevalence in unexposed	Reference	Denominator (from rate in literature)	Exposed: unexposed ratio	Sample size needed per cohort to detect specified RR							
					1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
MCM	3.0%	CDC 2008	Live births	1:1	2,627	796	413	265	190	146	117	97
SAB	11.8%	Wu et al. 2019	Pregnant women	1:1	596	177	90	57	40	30	24	19
Elective termination	20.6%	Jones et al. 2022	Pregnant women	1:1	300	87	43	26	18	13	9	NA
Gestational diabetes	6.9%	Martin 2021	Pregnant women	1:1	1,088	327	169	107	76	58	46	38
Gestational hypertension	6.5%	Butwick et al. 2020	Pregnant women	1:1	1,161	350	180	115	82	62	50	41
Pre-eclampsia	3.8%	Ananth et al. 2013	Pregnant women	1:1	2,054	622	322	206	148	113	91	75
Eclampsia	0.281%	Butwick et al. 2020	Live births	1:1	28,973	8,824	4,600	2,961	2,130	1,640	1,322	1,101
Stillbirth	0.596%	MacDorman and Gregory 2015	Live births and stillbirths	1:1	13,610	4,142	2,159	1,389	999	769	619	516
Preterm birth	8.47%	Martin et al. 2021	Singleton live births	1:1	868	260	134	85	60	46	36	30
SGA	10.0%	By definition	Singleton live births	1:1	721	215	110	70	49	37	29	24
Postnatal growth deficiency	10.0%	By definition	Singleton live births	1:1	721	215	110	70	49	37	29	24
Infant developmental delay	13%	Rosenberg et al. 2008	Live births	1:1	532	158	80	50	35	26	71	17

CDC = Centers for Disease Control and Prevention; MCM = major congenital malformation; NA = not applicable; RR = relative risk; SAB = spontaneous abortion; SGA = small for gestational age.
Calculations used SAS (version 9.4), Fisher's exact conditional test with Walters normal approximation method, assuming 80% power and 2-sided α of 0.05.

Table 5. Power Calculations With 364 Exposed and 364 Unexposed Pregnancies

Outcomes	Power Estimate (to Detect a Relative Risk of 3.0)
MCM	80%
SAB	>80%
Elective termination	>80%
Gestational diabetes	>80%
Gestational hypertension	>80%
Pre-eclampsia	>80%
Eclampsia	5.9%
Stillbirth	21.4%
Preterm birth	>80%
SGA	>80%
Postnatal growth deficiency	>80%
Infant developmental delay	>80%

MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age.

9.6. Data management

Data will be managed with an electronic data capture (EDC) platform that is compliant with 21 Code of Federal Regulations (CFR) Part 11. Variables will be solicited and entered in the EDC directly by participants or indirectly by VRCC staff. Data provided by participants and/or their HCPs over the phone or on paper data collection forms, which can be submitted to the VRCC via mail, e-mail or fax, will be reviewed for correctness and completeness and entered into the database by VRCC staff.

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

9.6.1. Data collection tools (DCTs)

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

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

PPD has ultimate responsibility for the collection and reporting of all data entered on the DCTs as required and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when

required. The DCT serves as the source document. Any corrections to entries made in the DCTs must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

9.6.2. Record retention

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

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

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

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

9.7. Data analysis

Detailed methodology for 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 endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Analysis population

The analysis population will include participants who:

- Are valid (Section 9.7.1.1)
- Are prospectively enrolled (Section 9.7.1.2)
- Are not exposed to teratogens or investigational medications during pregnancy (Section 9.7.1.3)
- Are not exposed to non-zavegepant CGRP medications (including CGRP antagonists and CGRP-related monoclonal antibodies) during pregnancy (Section 9.7.1.4)
- Are not considered lost to follow-up (Section 9.7.1.5)

For the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple-gestation pregnancies will be excluded from the analysis population (Section 9.7.1.7).

9.7.1.1. Valid versus invalid participants

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

9.7.1.2. Prospectively enrolled versus retrospectively enrolled participants

The registry will encourage prospective registration; however, retrospective enrollment in the registry will be permitted as well. A prospectively enrolled participant is defined as a pregnant individual who enrolls prior to the pregnancy outcome. A retrospectively enrolled participant is defined as a pregnant individual who enrolls after the pregnancy outcome has occurred.

Retrospectively enrolled participants can introduce bias toward the reporting of more unusual and severe outcomes and are less likely to be representative of the general population than prospectively enrolled participants. They may also recall past drug exposures differently compared to prospectively enrolled patients. Therefore, retrospectively enrolled participants will be excluded from the analysis population but will be included in supplementary analyses.

Diagnostic prenatal tests (eg, ultrasound to scan for structural defects at approximately 20 gestational weeks, chorionic villus sampling, and amniocentesis) can determine with high accuracy whether a fetus has a structural or chromosomal abnormality. Therefore, inclusion of individuals who have had diagnostic prenatal testing in the analysis population may introduce bias. To examine this potential bias, a sensitivity analysis that applies a stricter definition of prospective enrollment will be conducted. For this analysis, individuals who enroll prior to diagnostic prenatal testing will be considered prospectively enrolled, and individuals who enroll after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled. The outcomes of individuals who enroll prior to diagnostic prenatal testing will be compared with those of individuals who enrolled after diagnostic prenatal testing.

9.7.1.3. Participants exposed to teratogens or investigational medications

Participants will be considered exposed to teratogens or investigational medications during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (time period equivalent to 5 times the product's half-life). A list of teratogens (Annex 5) has been developed and will be continually updated based on the data available in the Teratogen Information System (TERIS) database of teratogenic agents and publications (Polifka 2002; Feldkamp 2015; TERIS 2021). Investigational medications

include drugs that are not yet approved by the FDA. Participants who are exposed to teratogens or investigational medications during pregnancy will be excluded from the analysis population but will be included in supplementary analyses.

9.7.1.4. Participants exposed to non-zavegepant CGRP medications

If women in either cohort are exposed to other CGRP medications (ie, other CGRP antagonists or CGRP-related monoclonal antibodies), interpreting results and detecting a possible safety signal for zavegepant will be challenging because these therapies are the same drug class as zavegepant.

Women will be considered exposed to other CGRP medications during pregnancy if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (time period equivalent to 5 times the product's half-life). Participants who are exposed to non-zavegepant CGRP medications during pregnancy will be excluded from the analysis population but will be included in supplementary analyses.

9.7.1.5. Participants lost to follow-up

A participant will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnant individuals without pregnancy outcome information and live-born infants without follow-up data after birth will be considered lost to follow-up. Annex 4 provides more information on the circumstances under which participants will be considered lost to follow-up. Information from these participants (eg, demographic characteristics, abnormal prenatal test results, and reason for loss to follow-up, if available) will be summarized in each registry report, but these participants will be excluded from the analysis population. While infants who are lost to follow-up will not contribute to the analysis of infant outcomes after the point in which they were lost to follow-up, the pregnancy information from their mothers will be included in the analysis of pregnancy outcomes. In addition, the proportion of participants who are lost to follow-up will be compared between the internal cohorts to assess any potential differential loss to follow-up which could bias the comparative analyses.

9.7.1.6. Subsequent pregnancies

Individuals who have previously enrolled in the registry with a prior pregnancy may enroll in the registry with subsequent pregnancies and contribute multiple pregnancies to the analysis population. Statistical non-independence due to multiple pregnancies from the same individual will be addressed in the analysis.

9.7.1.7. Multiple-gestation pregnancies

Multiple-gestation pregnancies will be enrolled in the registry and included in the analysis population; however, for the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple-gestation pregnancies will be excluded from the analysis population due to the higher risk of these outcomes in twins and higher-order multiples.

9.7.2. Descriptive characteristics

Participant characteristics (including the covariates listed in Section 9.3.5) will be summarized with descriptive statistics for each cohort.

The number of observations, median, mean, standard deviation, minimum, and maximum will be reported for each continuous variable. The frequency and percentage per category will be reported for each categorical variable.

For comparative analyses, balance between the internal cohorts will be assessed by calculating the standardized mean differences for all covariates, comparing the zavegepant exposed and zavegepant unexposed internal cohorts. These standardized mean differences will be presented before and after inverse probability of treatment weighting (IPTW).

9.7.3. Outcome prevalence

Prevalence of the outcomes of interest will be calculated according to the conventions described in Table 6. In general, the prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge.

For most outcomes, the analysis population (denominator) will be the number of pregnant individuals with pregnancy outcome data, the number of live births, or the number of infants with follow-up data at the timepoint of interest, as appropriate; however, for some outcomes, the analysis population (denominator) will be restricted based on certain relevant factors (as noted in Table 6).

Table 6. Outcome Prevalence Calculations

Outcome	Numerator (among those in denominator)	Denominator	Relevant etiologic period (timing of exposure assessment)
MCM	Live births with confirmed (ie, adjudicated) MCMs (excluding MCMs not associated with medication exposure)	Live births	First trimester
MCM sensitivity analysis (see Section 9.7.7.2)	Live births and fetal losses with confirmed MCMs (excluding MCMs not associated with medication exposure)	Live births and fetal losses	First trimester
SAB	Spontaneous abortions	Individuals with pregnancy outcome data who are enrolled before 20 completed gestational weeks	Before 20 completed gestational weeks
Elective termination	Elective terminations	Individuals with pregnancy outcome data	Before 20 completed gestational weeks

Table 6. Outcome Prevalence Calculations

Outcome	Numerator (among those in denominator)	Denominator	Relevant etiologic period (timing of exposure assessment)
Gestational diabetes	Pregnant individuals with gestational diabetes	Individuals with pregnancy outcome data	Full pregnancy period
Gestational hypertension	Pregnant individuals with gestational hypertension	Individuals with pregnancy outcome data	Full pregnancy period
Pre-eclampsia	Pregnant individuals with pre-eclampsia	Individuals with pregnancy outcome data	Full pregnancy period
Eclampsia	Pregnant individuals with eclampsia	Individuals with pregnancy outcome data	Full pregnancy period
Stillbirth	Stillbirths	Individuals with pregnancy outcome data	Full pregnancy period
Preterm birth	Preterm births	Singleton live births without confirmed MCM among pregnant individuals who are enrolled before 37 completed gestational weeks	Before 37 completed gestational weeks
SGA	SGA births	Singleton live births without confirmed MCM with weight data	Full pregnancy period
Minor congenital malformations	Live births with minor congenital malformation	Live births	Full pregnancy period
Postnatal growth deficiency (at 2, 4, 6, and 12 months)	Infants with postnatal growth deficiency	Singleton live births without confirmed MCM, preterm birth, or SGA with weight/length/head circumference data at the specified timepoint	Full pregnancy period
Infant developmental delay (at 2, 4, 6, and 12 months)	Infants with developmental delay	Live births without confirmed MCM or preterm birth with developmental milestone data for the category at the specified timepoint	Full pregnancy period

MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small-for-gestational-age.

9.7.4. Comparative analyses

Comparative analyses will be conducted for each outcome using the internal cohorts. Crude (unadjusted) RRs (and corresponding 95% CIs) will be calculated using Exact methods. Adjusted RRs will be calculated using generalized linear models (binomial family) with a log (RR) link and weighted by IPTW (Desai and Franklin 2019). The Clopper-Pearson method will be used to derive 95% CIs.

9.7.4.1. Propensity score modeling

Inverse probability of treatment weights will be calculated using propensity scores estimated from propensity score models (Desai and Franklin 2019). Each individual's propensity score (the probability of being in the internal exposed cohort, given membership in the study

population [either internal cohort]) will be estimated using a logistic regression model with exposure status as the outcome (dependent variable). The covariates listed in Section 9.3.5 will be considered for inclusion in the model as independent (predictor) variables. Only covariate information from prior to pregnancy start (conception) will be included in propensity score models. Each variable will be carefully considered by the investigators to ensure that only potential risk factors (and therefore potential confounders) for the study outcomes are included in the final propensity score model.

Stabilized weights will be estimated with trimming at the first and 99th percentiles to minimize the impact of any extreme weights (Stuart 2010; Hernán and Robbins 2020). One propensity score model will be developed that includes all participants in the internal study cohorts (ie, zavegepant exposed and comparators). Hence, each participant will have one estimated propensity score for all analyses.

9.7.4.2. Comparison with external nonmigraine cohort and other external prevalence estimates

Exact methods will be used to compare the observed outcome prevalence in the internal study cohorts to the external nonmigraine cohort and to other data sources (eg, MACDP, EUROCAT, national vital statistics, published literature), as applicable. These comparisons will be crude.

For these external comparisons, the prevalence will be calculated according to the conventions used by the selected external comparators. For example, for comparison with MACDP, live births and stillbirths with MCMs, including MCMs not associated with medication exposure, will be included in the numerator, and the denominator will be the number of live births.

9.7.5. Subgroup analyses

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

- Timing of exposure (earliest trimester of exposure)
- Extent of exposure (cumulative dose during pregnancy [similar to duration for acute treatments], or relevant exposure window)
- Maternal age group at conception (15 to <18, 18 to <35, 35 to <45, and ≥45 years)
- Migraine severity

In addition, for the primary outcome MCM, a subgroup analysis will be conducted by the organ system of the defect.

9.7.6. Supplementary analyses

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

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

- Exposure to a known teratogen or an investigational medication during pregnancy (teratogen/investigational medication-exposed participants)
- Exposure to a non-zavegepant CGRP medication during pregnancy (non-zavegepant CGRP medication-exposed participants)

9.7.7. Sensitivity analyses

The following sensitivity analyses will also be conducted to examine the extent to which changes in certain methods or assumptions affect the results, if sample size permits, and presented in the final study report.

9.7.7.1. Definition of prospective enrollment

As described in Section 9.7.1.2, a sensitivity analysis of MCM will be conducted that applies a stricter definition of prospective enrollment. For this analysis, individuals who enroll prior to diagnostic prenatal testing will be considered prospectively enrolled, and individuals who enroll after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled. The outcomes of individuals who enroll prior to diagnostic prenatal testing will be compared with those of individuals who enrolled after diagnostic prenatal testing.

9.7.7.2. Inclusion of fetal losses in MCM denominator

As described in Table 6, a sensitivity analysis will be conducted that broadens the MCM denominator to include fetal losses in addition to live births.

9.7.7.3. Restriction of exposed cohort to participants exposed to zavegepant only

The internal zavegepant-exposed cohort will be restricted to the subset of patients that are exposed to zavegepant only, and no other acute or preventive migraine treatments during pregnancy.

9.7.7.4. Restriction of internal comparator cohort to treated participants

The internal comparator cohort will be restricted to the subset of individuals exposed to at least one migraine therapy. As noted in Section 9.2.4, this will be the main analysis rather than a sensitivity analysis if adequately powered.

9.7.7.5. Restriction of internal study cohorts to participants with a pre-pregnancy diagnosis of migraine

The internal study cohorts will be restricted to the subset of individuals with a diagnosis of migraine prior to the date of conception.

9.7.8. Missing data

The frequency and percentage of participants with missing data will be presented for each variable. Propensity scores may be calculated for all individuals, even those with missing data since the models can incorporate missing indicators. If the proportion of missing data is large, missing data methods may be considered, such as multiple imputation.

9.8. Quality control

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

9.8.1. Steering Committee

A steering committee will be established to oversee the scientific affairs of the study, including its ongoing monitoring. A charter for steering committee activities, roles and responsibilities, and meeting frequency will be established following study initiation. The steering committee will be composed of recognized experts including (but not limited to) the fields of teratology, epidemiology, maternal-fetal medicine, neonatology/pediatrics, and migraine treatment. The steering committee and birth defect evaluators will be independent of one another.

The steering committee will meet regularly to review the accumulated body of data from the study, including review of reported MCMs, which have been classified by independent birth defect evaluators, and other study outcomes. The steering committee will provide consultation regarding recruitment and retention strategies and will also carry out any actions required, including review and interpretation of data analyses and reports and contribute to publications of study data. In addition to the above activities, the steering committee will support the design and implementation of strategies to heighten awareness of the study.

9.9. Limitations of the research methods

This registry will aim to primarily collect data prospectively, minimizing the potential impact of recall bias. With primary data collection, rich, detailed information can be collected on participants, their pregnancies, and their infants, including information that is not routinely captured in medical records. Furthermore, direct data capture from participants and HCPs may minimize potential exposure, outcome, and covariate misclassification. Nonetheless, this study is subject to several limitations.

Many individuals avoid medications during pregnancy and the safety of zavegepant use in pregnancy is currently unknown. Hence, the number of enrolled zavegepant-exposed participants may be small, precluding the ability to calculate precise RRs or derive meaningful conclusions. A multi-model recruitment campaign and flexible, evolving retention strategies will aim to maximize study size (Annex 2).

Early, prospective enrollment is key to reducing recall and selection bias, however early pregnancy losses may be less likely to be included in a registry. Indeed, research suggests that 90% of pregnancies enrolled in registries result in a live birth (Covington et al. 2010; Veley et al. 2020) whereas national estimates suggest up to 28% of pregnancies end in early losses (ie, ~70% result in a live birth) (Rossen et al. 2018). Selection bias may also be

introduced if participants who are lost to follow-up are systematically different from participants that complete the study.

Despite limiting the main analysis to prospectively enrolled participants, voluntary participation could still produce bias (eg, if high- or low-risk individuals are more likely to enroll). A description of participant characteristics including comorbidities and pregnancy history will help assess the extent of such possible bias.

Some outcome risk factors may be unbalanced between the exposed and unexposed study cohorts. Propensity scores will be employed to statistically adjust for any baseline differences between cohorts. However, only measured covariates will be factored into the analysis and the potential for residual confounding remains due to unmeasured or poorly measured confounders.

There is a potential for confounding by indication where individuals with greater migraine severity or frequency are more or less likely to use zavegepant. This type of confounding can be statistically adjusted for using propensity scores, but only if accurate information on migraine severity and frequency is measured. HCPs and/or participants will provide details regarding migraine severity and participants will provide weekly/monthly migraine logs, but this information may be missing for some participants.

Even with primary data collection of migraine therapy details at multiple time points during pregnancy from the participant and their HCP (Section 9.3.3), exposure misclassification may occur. For example, the HCP may know the prescription date, dose, and route, but will not know exactly when the participant used the medication (eg, for as-needed rather than daily treatment). Further, participants will complete a migraine log with therapy details but will need to recall such details for the period of time between the first day of the last menstrual period and enrollment.

The primary outcome, MCM, is a heterogenous composite of any type of MCM. Individual drugs are more likely to have effects on specific MCM subtypes than all MCMs. However, the study is not powered to detect increases in the risk of individual defects.

While a sensitivity analysis is planned to assess the occurrence of MCMs in fetal losses, the condition of the lost fetus and the exact nature of MCM may be unknown. The data collection form will retrieve any information available, but this information is expected to be limited. Hence, outcome misclassification may be more likely for MCMs among fetal losses than for MCMs among livebirths. Data for all study outcomes will be reported by the HCPs, minimizing potential outcome misclassification; however, outcome misclassification is possible.

Although the external nonmigraine cohort will provide useful context, it cannot be directly compared to the internal study cohorts. The external cohort will include women identified in a database comprised of commercially insured women where data is collected for healthcare administrative purposes. The internal study cohorts will include women with and without health insurance for whom data is collected by the participants and their HCPs for this study. Hence, comparative analyses will be limited to the internal cohorts.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Study participant information

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

Participant personal data will be stored at PPD in an electronic portal or secured in a locked room to ensure that only authorized study staff have access. PPD will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, PPD shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

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

10.2. Participant consent

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

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

guardian(s) will be obtained in the US states in which this is required by local laws and regulations.

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

10.2.1. Additional safeguards for children in clinical investigations

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

10.2.2. Electronic informed consent process

The website will contain information about the registry and will provide access to the study's web-based/mobile application. The individual will register with their computer or mobile device using credentials (ie, name, e-mail address, and password) via the web-based/mobile application.

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

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

The application will provide an option for the individual to view or e-mail their completed consent form(s).

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

10.2.3. Waiver of documentation of informed consent

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

As is stated in US CFR (FDA 2022), 21 CFR 56.109 [and additionally in 45 CFR 46.117(c)(2)]:

> (c) An IRB shall require documentation of informed consent in accordance with 50.27 of this chapter, except as follows:
>
> > (1) The IRB may, for some or all subjects, waive the requirement that the subject, or the subject's legally authorized representative, sign a written consent form if it finds that the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside the research context
>
> (d) In cases where the documentation requirement is waived under paragraph (c)(1) of this section, the IRB may require PPD to provide subjects with a written statement regarding the research.

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

1. An adequate plan is provided to protect the identifiers from improper use and disclosure.
2. An adequate plan is provided to remove the identifiers at the earliest opportunity.
3. Adequate assurances are provided that the protected health information will not be reused or disclosed to any other person or entity.

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

10.3. Participant withdrawal

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

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

10.4. Institutional review board (IRB)/independent ethics committee (IEC)

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

10.5. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in the following guidelines:

- Guidelines for Good Pharmacoepidemiology Practices (GPP). Public Policy Committee, International Society of Pharmacoepidemiology. Pharmacoepidemiology and Drug Safety 2015; 25:2-10. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.3891
- Postapproval Pregnancy Safety Studies: (Draft) Guidance for Industry issued by FDA https://www.fda.gov/media/124746/download
- International Ethical Guidelines for Epidemiological Studies issued by the Council for International Organizations of Medical Sciences (CIOMS) https://cioms.ch/shop/product/international-ethical-guidelines-for-epidemiological-studies/
- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology http://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml
- Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ ucm071696.pdf
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidance s/UCM243537.pdf

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

Table 7 summarizes the requirements for recording safety events on the data collection form and for reporting safety events on the NIS AEM Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: 1) serious AEs; 2) non-serious AEs (as applicable); and 3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure. These events are defined in Section 11.3 (Definitions of Safety Events).

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

Table 7. Safety Event Reporting Requirements

Safety Event	Recorded on the data collection forms	Reported on the NIS AEM Report Form to Pfizer Safety within 1 Business Day/3 Calendar Days[a] of Awareness
Serious AE	All	All[b]
Non-serious AE	All	None
Scenarios involving exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy	All (regardless of whether associated with an AE)	All (regardless of whether associated with an AE/serious AE) Note: Any associated AE is reported together with the exposure scenario.
Scenarios involving EDP	All AEs or serious AEs associated with EDP Notification of EDP alone (ie, not associated with an AE or serious AE) is not required when the study population is pregnant individuals.	All serious AEs[b] associated with EDP Notification of EDP alone (ie, not associated with a serious AE) is not required when the study population is pregnant individuals.
Scenarios involving occupational/environmental exposure	Not applicable	All (regardless of whether associated with an AE/serious AE)

AE = adverse event; AEM = adverse event monitoring; EDP = exposure to a drug during pregnancy; NIS = non-interventional study.
a Whichever is shorter. If a national or state holiday falls directly before or after a weekend (resulting in ≥3 consecutive calendar days of closure), the reporting will be done the next business day.
b Except for serious AEs judged by External Adjudication Committee [ie, any malformations]). Of note, adjudicated serious AEs of which an HCP has indicated the serious AE to have a causal relationship with zavegepant or other medications used to treat migraine are not included within this exception and must be reported to Pfizer Safety.

For each safety event, the PPD VRCC must pursue and obtain adequate information to determine the outcome and to assess whether it meets the criteria for classification as a serious AE (refer to Section 11.3.2 Serious Adverse Events).

Safety events must be reported per the process noted in Table 7 **regardless of whether the event is determined by the HCP to be related to zavegepant**. In particular, if the serious AE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. The timeframe noted in Table 7 also applies to additional, new (follow-up) information on previously forwarded safety event reports. In the rare situation that the PPD VRCC does not become immediately aware of the occurrence of a reportable safety event, the PPD VRCC must report the event within 1 business day/3 calendar days after learning of it and document the time of first awareness of the events on the NIS AEM Report Form.

For all safety events that are mentioned in the far-right column of Table 7, the PPD VRCC is obligated to pursue and to provide any additional information to Pfizer with the same reporting timeline. In addition, the PPD VRCC may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the data collection forms. In general, this will include a description of the safety event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

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

11.1. Reporting period

For each patient, the reporting period will begin at the time of the patient's first dose of zavegepant or other medications used to treat migraine, or the time of the patient's informed consent if she is being treated with zavegepant or other medications used to treat migraine at study start, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of the drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any safety events (as per Table 7) occurring during this period. If a patient is administered zavegepant or other medications used to treat migraine on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some

situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation, failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient.

If the PPD VRCC becomes aware of a serious AE occurring at any time after completion of the study and the serious AE has been reported as related to zavegepant or other medications used to treat migraine, the serious AE also must be reported to Pfizer Safety.

11.2. Causality assessment

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

In this study, unlike a trial design with sites and investigators, reporting HCPs will not have received formal training on providing causality assessments for the study drug. Further, given limited known information about the safety of zavegepant in pregnancy, it is expected that the HCPs will rarely provide a causality assessment for the reportable safety events, or they will report it as "unknown" as s/he cannot determine it. In this event, the applicable, reportable safety event must still be reported to Pfizer Safety per the process outlined in Table 7.

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

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

11.3. Definitions of safety events

11.3.1. Adverse events

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

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

- Lack of efficacy
- Drug abuse
- Drug dependency

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

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

Abnormal test findings

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

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

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

11.3.2. Serious adverse events

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

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

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

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

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

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

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

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

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

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

Exposure during pregnancy

An EDP occurs if:

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

This information must be submitted to Pfizer Safety following the same reporting timeline and using the NIS AEM Report Form and the EDP Supplemental Form. Prospective and retrospective exposure during pregnancy reports are reportable to Pfizer Safety following the requirement described in Table 7.

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

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

If the outcome of the pregnancy meets the criteria for a serious AE (e.g., ectopic pregnancy, SAB, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting serious AEs should be followed.

Additional information about pregnancy outcomes that are reported as serious AEs follows:

- SAB includes miscarriage and missed abortion
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as serious AEs. In addition, infant deaths after 1 month should be reported as serious AEs when the HCP assesses the infant death as related or possibly related to exposure to investigational product.

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

For NIS conducted in pregnant individuals, data on the pregnancy outcome and non-serious AEs are expected to be collected and analyzed in the study database. In such instances, only EDPs associated with a SAE are to be reported.

Exposure during breastfeeding

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

Medication error

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

Medication errors include:

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

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

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

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

Overdose, misuse, extravasation

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

Lack of efficacy

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

Occupational/Environmental exposure

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

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

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if PPD 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.

In addition, PPD will inform Pfizer immediately of any urgent safety measures taken by PPD to protect the study participants against any immediate hazard, and of any serious breaches of this NIS protocol of which PPD becomes aware.

The registry will produce annual interim progress reports, and a final comprehensive study report will be developed after the conclusion of the registry.

Each annual interim report will present the registry design, methodology, and results to date, including the number of enrolled participants, their demographics and characteristics, and

their outcomes, by study cohort. As needed, strategies will be considered to support increased enrollment and improved representativeness. The 4th annual interim report in 2028 will include a feasibility assessment that discusses the potential to meet enrollment targets within the US.

The final comprehensive study report will present the results of the full statistical analysis (described in Section 9.7) as well as an interpretive discussion of the results.

Annual interim and final study reports will be submitted to the relevant regulatory agencies. Submissions to scientific congresses and/or to peer-reviewed journals are planned. Additionally, this study will be disclosed and registered in the European Union electronic register of Post-Authorisation Studies (EU PAS Register).

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14. LIST OF TABLES

15. LIST OF FIGURES

16. ANNEX 1. LIST OF STAND ALONE DOCUMENTS

EXTERNAL NONMIGRAINE COHORT DRAFT PROTOCOL (C5301027, “Observational Cohort Study of Zavegepant Safety in Pregnancy Within a US Claims Database”)

17. ANNEX 2. RECRUITMENT AND RETENTION STRATEGY

17.1. Recruitment strategy

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

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

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

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

17.2. Diversity

Study materials (eg study website, data collection forms, information sheet, and informed consents) will be available in US English and US Spanish. In addition, a translation vendor will be available to engage in real-time translation for existing and potential participants. Campaign materials will also depict a diversity of individuals and families. Efforts will be made to recruit a patient population that is representative of the racial and ethnic distribution of individuals with migraine.

17.3. Direct-to-HCP outreach

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

17.4. Digital advertising

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

- FDA listing of pregnancy registries on www.fda.gov
- EU PAS register
- Pfizer website
- PPD website (https://www.ppd.com/our-solutions/clinical/peri-and-post-approval/non-interventional-studies/pregnancy-and-lactation-studies/)

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

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

17.5. Print advertising

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

17.6. Recruitment materials

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

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

17.7. Retention strategy

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

The registry staff will serve as the first and single point of communication for registry participants and HCPs. The specialized staff, many of whom are obstetric nurses, have experience collecting data for observational studies from patients and research-naïve HCPs. They are experts at developing a rapport with HCPs and participants to facilitate data collection and build one-on-one relationships that will promote retention and reduce overall loss to follow-up. To promote HCP engagement, status updates may be shared with HCPs through various means (ie, e-mail, newsletters, and the registry website). Materials provided will emphasize the mission of the registry to promote participant engagement and point participants to the website.

The registry will use streamlined data collection processes and simple, concise data collection forms that focus on endpoints of interest to reduce the burden of reporting. The registry will provide multiple options for communication and data submission (eg, phone, fax, mail, e-mail, website, web-based/mobile application) and a flexible follow-up schedule to enhance retention and maximize data reporting.

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

17.8. Assessment of recruitment and retention

To maximize recruitment and retention, the registry's recruitment and retention strategies will be flexible and will be continuously assessed. The registry will assess recruitment and retention by collecting information from reporters (ie, HCPs and participating individuals) on

the sources from which they received information about the registry (recruitment) and the reasons for which they ceased participation or were lost to follow-up (retention). Based on these assessments, the registry's recruitment and retention strategies will be adjusted to maximize registry participation.

18. ANNEX 3. MIGRAINE TREATMENTS

This list will be updated throughout the course of the study as new products are approved.

Table 8. List of Migraine Therapies

Drug class	Generic name	Acute or preventive	Half-life
ACE inhibitors	Enalapril	Preventive	11 h
	Lisinopril	Preventive	12 h
	Ramipril	Preventive	13 to 17 h
Anticonvulsants	Carbamazepine*	Preventive	10 to 65h
	Gabapentin	Preventive	6.5 h
	Levetiracetam	Preventive	6 to 8 h
	Topiramate*	Preventive	21 h
	Valproic acid, Valproate*	Preventive	9 to 16 h
Anti-depressants	Amitriptyline	Preventive	10 to 28 h
	Bupropion	Preventive	3 to 4 h
	Citalopram	Preventive	35 h
	Doxepin	Preventive	15.3 h
	Duloxetine	Preventive	8 to 17 h
	Escitalopram	Preventive	27 to 32 h
	Fluoxetine	Preventive	24 to 96 h
	Nefazodone	Preventive	2 to 4 h
	Nortriptyline	Preventive	26 h
	Paroxetine	Preventive	21 to 24 h
	Sertraline	Preventive	24 to 32 h
	Trazodone	Preventive	10 to 12 h
	Venlafaxine	Preventive	3 to 4 h
Antihistamines	Chlorpheniramine	Acute	20 h
	Cyproheptadine	Acute	8 h
	Diphenhydramine	Acute	3.4 to 9.2 h
	Phenyltoloxamine	Acute	NA
Anti-nauseants	Aprepitant	Acute	9 to 13 h
	Chlorpromizine	Acute	23 to 37 h
	Granisetron	Acute	8.9 h
	Meclizine	Acute	5 to 6 h
	Metoclopramide	Acute	5 to 6 h
	Ondansetron	Acute	2.8 to 4.8 h
	Palonosetron	Acute	40 h
	Prochlorperazine	Acute	9 h
	Rolapitant	Acute	135 to 231 h
	Tolazamide	Acute	7 h
Antipsychotics	Aripiprazole	Acute	75 h
	Haloperidol	Acute	14 to 37 h
	Olanzapine	Acute	21 to 54 h

Table 8. List of Migraine Therapies

Drug class	Generic name	Acute or preventive	Half-life
	Paliperidone	Acute	24 h
	Quetiapine	Acute	6 h
	Risperidone	Acute	3 to 20 h
ARBs	Candesartan	Preventive	9 h
	Telmisartan	Preventive	24 h
Barbiturates	Butalbital	Acute	35 h
	Phenobarbital	Acute	100 h
Benzodiazepines/Sedatives	Clonazepam	Preventive	30 to 40 h
	Diazepam	Preventive	48 h
	Lorazepam	Preventive	12 h
	Meprobamate	Acute	1.7 to 2 h
Beta-blockers	Atenolol	Preventive	6 to 7 h
	Bisoprolol	Preventive	9 to 12 h
	Carvedilol	Preventive	7 to 10 h
	Esmolol	Preventive	9 m
	Labetalol	Preventive	6 to 8 h
	Metoprolol	Preventive	3 to 4 h
	Nadolol	Preventive	20 to 24 h
	Pindolol	Preventive	2.5 to 30 h
	Propranolol	Preventive	3 to 6 h
	Timolol	Preventive	3.5 to 4.5 h
Botox	Botulinum toxin type A	Preventive	4 h
	Botulinum toxin type B	Preventive	NA
Calcium channel blockers	Flunarizine	Preventive	5 to 15 h (terminal 18 to 19 d)
	Nimodipine	Preventive	8 to 9 h
	Verapimil	Preventive	2 to 5 h
CGRP antagonists	Atogepant	Preventive	11 h
	Rimegepant	Acute and preventive	11 h
	Ubrogepant	Acute	5 to 7 h
	Zavegepant	Acute	6.5 h
CGRP monoclonal antibodies	Eptinezumab	Preventive	27 d
	Erenumab	Preventive	28 d
	Fremanezumab	Preventive	31 d
	Galcanezumab	Preventive	27 d
Complementary medications	Butterbur (petasites)	Preventive	4 to 6 h
	Caffeine	Acute	1.5 to 9.5 h
	Co-Q10	Preventive	33 h
	Feverfew (MIG-99)	Preventive	NA
	Magnesium sulfate	Acute	2.7 to 5.2 h
Ditans	Lasmiditan	Acute	5.7 h

Table 8. List of Migraine Therapies

Drug class	Generic name	Acute or preventive	Half-life
Ergotamine	Dihydroergotamine	Acute	10 to 13 h
	Ergotamine	Acute	2 to 2.5 h
Muscle relaxants	Carisoprodol	Acute	1.7 to 2 h
	Methocarbamol	Acute	1 to 2 h
	Orphenadrine	Acute	13 to 20 h
Neuromodulation	Non-invasive multi-channel brain neuromodulation system	Acute	NA
	Single Pulse Transcranial Magnetic Stimulator	Acute	NA
	Transcutaneous Supraorbital Neurostimulator	Acute	NA
	Transcutaneous Vagus Nerve Stimulator	Acute	NA
Pain therapies: opioids/narcotics	Buprenorphine	Acute	25 to 70 h
	Butorphanol	Acute	18 h
	Codeine	Acute	2.5 to 3 h
	Dezocine	Acute	1.2 to 7.4 h
	Dihydrocodeine	Acute	3.8 h
	Ethoheptazine	Acute	NA
	Fentanyl	Acute	3 to 7 h
	Hydrocodone	Acute	3.8 h
	Hydromorphone	Acute	8 to 15 h
	Hydroxycodeine	Acute	3.8 h
	Levomethadyl	Acute	62.4 h
	Levorphanol	Acute	11 to 16 h
	Meperidine	Acute	2 to 5 h
	Methadone	Acute	8 to 59 h
	Morphine	Acute	2 to 4 h
	Nalbuphine	Acute	5 h
	Opium	Acute	NA
	Oxycodone	Acute	3 h
	Oxymorphone	Acute	7.2 to 9.4 h
	Pentazocine	Acute	2 to 4 h
	Propoxyphene	Acute	6 to 12 h
	Sufentanil	Acute	2.7 h
	Tapentadol	Acute	6 h
	Tramadol	Acute	7 h
Pain therapies: NSAIDs	Acetaminophen	Acute	1 to 3 h
	Aspirin	Acute	0.3 h
	Celecoxib	Acute	11 h
	Diclofenac	Acute	2 h
	Diflunisal	Acute	8 to 12 h
	Etodolac	Acute	6.5 h

Table 8. List of Migraine Therapies

Drug class	Generic name	Acute or preventive	Half-life
	Fenoprofen	Acute	3 h
	Flurbiprofen	Acute	4.7 to 5.7 h
	Ibuprofen	Acute	1.9 to 2.2 h
	Indomethacin	Acute	4.5 h
	Ketoprofen	Acute	2 to 2.5 h
	Ketorolac	Acute	5 to 6 h
	Mefenamic acid	Acute	2 h
	Meloxicam	Acute	20 h
	Nabumetone	Acute	19 to 36 h
	Naproxen	Acute	12 to 17 h
	Oxaprozin	Acute	40 to 60 h
	Piroxicam	Acute	50 h
	Salicylamide	Acute	1 h
	Sulindac	Acute	7.8 to 16.4 h
	Tolmetin	Acute	1 to 2 h
	Valdecoxib	Acute	8 to 11 h
Pain therapies: other	Dipyridamole	Acute	0.6 h
	Phenacetin	Acute	0.6 to 1.2 h
	Pseudoephedrine	Acute	6 h
Steroid	Corticosteroids	Acute	18 to 36 h
Triptans	Almotriptan	Acute	3 to 4 h
	Eletriptan	Acute	5 h
	Frovatriptan	Acute	26 h
	Naratriptan	Acute	6 h
	Rizatriptan	Acute	2 to 3 h
	Sumatriptan	Acute	2.5 h
	Sumatriptan/Naproxen sodium	Acute	2.5 to 17 h
	Zolmitriptan	Acute	3 h

ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers; CGRP = calcitonin gene-related peptide, NA = not applicable

19. ANNEX 4. REGISTRY DATA COLLECTION DETAILS

19.1. Information collected at enrollment

After obtaining informed consent, the following information will be collected on the ***Registration Form for Participants***, ***Registration Form for Healthcare Providers***, ***Weekly Log for Migraine Headaches and Acute Medications***, ***Monthly Log for Preventive Migraine Medications,*** and ***Pregnancy Information Form***:

Table 9. Information Collected at Enrollment

Data	Collected from Participants	Collected from HCPs
Reporter information	• Contact information for the participant, as well as alternate contact information • HCP reporter contact information (pediatric HCP information may be provided around time of EDD if unknown at enrollment) • Request for Release of Medical Information Form(s) (form may be completed for pediatric HCP around time of EDD if unknown at enrollment)	
Registration information	• Date of consent (enrollment) • Recruitment source(s) • Minimum data for study cohort assignment: ○ Country of residence ○ Pregnancy status ○ Migraine diagnosis information ○ Exposure information ○ Prior enrollment status	• Minimum data for study cohort assignment: ○ Pregnancy status ○ Migraine diagnosis information ○ Exposure information
Maternal demographics	• Maternal demographics ○ Race and ethnicity[a] ○ Marital status ○ Insurance status ○ Education ○ Employment status ○ Income	

Table 9. Information Collected at Enrollment

Data	Collected from Participants	Collected from HCPs
Baseline pregnancy information		• First day of LMP • Method of conception
Migraine information	• Maternal history of migraine, including date of diagnosis • Characteristics of migraine, including measures of disease severity prior to pregnancy • Dates of migraine headaches during pregnancy (in real-time or near real-time during pregnancy)	• Maternal history of migraine, including date of diagnosis
Maternal pre-pregnancy anthropomorphics		*If not available from HCP, can be collected from participant* • Pre-pregnancy anthropometrics (weight and height)
Maternal obstetrical history		*If not available from HCP, can be collected from participant* • Number of previous pregnancies (singleton or multiple) • Outcome of all previous pregnancies • Complications of previous pregnancies • Characteristics of previous live births (preterm, SGA) • History of offspring with congenital anomalies
Family history of congenital malformations		*If not available from HCP, can be collected from participant* • Maternal and paternal history of congenital anomalies
Maternal past medical history		*If not available from HCP, can be collected from participant* • Past maternal medical conditions, including but not limited to thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders (eg, substance abuse disorder), hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (eg, congenital uterine abnormalities)
Maternal exposures during pregnancy	• On a weekly basis, exposure to zavegepant or other acute migraine therapies (prescription and non-prescription), including name of product, dates of exposure, and total dose taken on each day of the week, if available (collected in real-time or near real-time during pregnancy) • On a monthly basis, exposure to zavegepant or other preventive migraine therapies (prescription and non-	• Exposure to drugs or biological products (including prescription and non-prescription drugs, dietary supplements, prenatal vitamins, folic acid, neuromodulation devices, vaccines, and known teratogens), including indication/reason for use (for migraine products - acute only, preventive only, or both), dose, route, frequency, and dates/duration of exposure

Table 9. Information Collected at Enrollment

Data	Collected from Participants	Collected from HCPs
	prescription), including name of product, dates of exposure, dose, route, and frequency (collected in real-time or near real-time during pregnancy)	• Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure
Ongoing pregnancy information		• Number of fetuses • EDD and method of determination • Prenatal tests performed, including type of test, date of test, and results/findings (eg, congenital malformations) • Concurrent maternal medical conditions, including but not limited to thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders (eg, substance abuse disorder), hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (eg, congenital uterine abnormalities) • Concurrent pregnancy-related maternal medical conditions or pregnancy complications

EDD = estimated date of delivery; HCP = healthcare provider; LMP = last menstrual period; SGA = small for gestational age.
a Race and ethnicity data will be collected in a manner consistent with the recommendations of the FDA guidance, "Collection of Race and Ethnicity Data in Clinical Trials and Clinical Studies for FDA-regulated Medical Products" (available from https://www.fda.gov/regulatory-information/search-fda-guidance-documents/collectionrace-nd-ethnicity-data-clinical-trials-and-clinical-studies-fda-regulated-medical)

19.2. Information collected at pregnancy follow-up

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

19.2.1. Follow-up at end of second trimester

Table 10. Information Collected at End of Second Trimester

Data	Collected from Participants	Collected from HCPs
Migraine information	• Dates of migraine headaches during pregnancy (collected in real-time or near real-time during pregnancy)	
Maternal exposures during pregnancy	• On a weekly basis, exposure to zavegepant or other acute migraine therapies (prescription and non-prescription), including name of product, dates of exposure, and total dose taken on each day of the week, if available (collected in real-time or near real-time during pregnancy) • On a monthly basis, exposure to zavegepant or other preventive migraine therapies (prescription and non-prescription), including name of product, dates of exposure, dose, route, and frequency (collected in real-time or near real-time during pregnancy)	• Exposure drugs or biological products (including prescription and non-prescription drugs, dietary supplements, prenatal vitamins, folic acid, neuromodulation devices, vaccines, and known teratogens), including indication/reason for use (for migraine products - acute only, preventive only, or both), dose, route, frequency, and dates/duration of exposure, if available • Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing of exposure, if available
Ongoing pregnancy information		• Number of fetuses • EDD and method of determination • Prenatal tests performed, including type of test, date of test, and results/findings (eg, congenital malformations) • Concurrent maternal medical conditions, including but not limited to thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders (eg, substance abuse disorder), hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (eg, congenital uterine abnormalities) • Concurrent pregnancy-related maternal medical conditions or pregnancy complications

EDD = estimated date of delivery; HCP = healthcare provider.

19.2.2. Follow-up at pregnancy outcome

Table 11. Information Collected at Pregnancy Outcome

Data	Collected from Participants	Collected from HCPs
Disease information	• Dates of migraine headaches during pregnancy (in real-time or near real-time during pregnancy)	
Maternal exposures during pregnancy	• On a weekly basis, exposure to zavegepant or other acute migraine therapies (prescription and non-prescription), including name of product, dates of exposure, and total dose taken on each day of the week, if available (collected in real-time or near real-time during pregnancy) • On a monthly basis, exposure to zavegepant or other preventive migraine therapies (prescription and non-prescription), including name of product, dates of exposure, dose, route, and frequency (collected in real-time or near real-time during pregnancy)	• Exposure drugs or biological products (including prescription and non-prescription drugs, dietary supplements, prenatal vitamins, folic acid, neuromodulation devices, vaccines, and known teratogens), including indication/reason for use (for migraine products - acute only, preventive only, or both), dose, route, frequency, and dates/duration of exposure • Exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs, including timing
Ongoing pregnancy information		• Number of fetuses • EDD and method of determination • Prenatal tests performed, including type, date, and results/findings • Concurrent maternal medical conditions, including but not limited to thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders (eg, substance abuse disorder), hepatitis, sexually transmitted diseases, and uterine or cervical abnormalities (eg, congenital uterine abnormalities) • Concurrent pregnancy-related maternal medical conditions or pregnancy complications
Pregnancy outcome information		• Pregnancy outcome (SAB, elective termination, live birth, stillbirth) • Date of outcome of pregnancy • Gestational age at outcome • Fetal/infant characteristics, including sex, birth weight, length, head circumference

Table 11. Information Collected at Pregnancy Outcome

Data	Collected from Participants	Collected from HCPs
		• Route of delivery • Delivery/birth complications if any • 5-minute Apgar score • Congenital malformation(s) and potential contributing factors ○ Includes any postmortem findings available for non-live pregnancy outcomes (SAB, stillbirths) with major congenital malformations (MCMs) • For a fetal loss (SAB, stillbirth), factors that may have had an impact on the loss • For elective termination, reason

EDD = estimated date of delivery; HCP = healthcare provider.

19.3. Information collected at pediatric follow-up

Timing of pediatric follow-up

If a live birth occurs, the mother is asked to provide authorization for medical release for the infant's pediatric HCP to provide follow-up information. If authorization for medical release is obtained, the pediatric HCP will be asked to complete the ***Infant Outcomes Form*** at 4 and 12 months of age. At approximately 4 months after delivery, infant data at 2 and 4 months of age will be collected; at approximately 12 months after delivery, infant data at 6 and 12 months of age will be collected. To reduce recall bias, pediatric HCPs will be asked to provide data that are routinely documented in the infants' medical records at their visits at 2, 4, 6, and 12 months of age. This schedule follows the American Academy of Pediatrics infant well-child visit schedule (AAP 2022).

Table 12. Information Collected at Pediatric Follow-up

Data	Collected from HCPs
Infant outcome information	• Date of follow-up evaluation • Age of infant • Weight, length, head circumference of infant • Developmental milestones per the HCP's assessment of normal, delayed, etc. • Congenital malformation(s) and potential contributing factors • Infant death, including date and cause of death

HCP = healthcare provider.

19.4. Targeted follow-up after report if an event of interest

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

Table 13. Targeted Follow-up after Event of Interest Reported

Data	Collected from HCPs
Targeted follow-up information	• Details of the congenital malformation or other event of interest • Etiology • Maternal infections/conditions of relevance to event • Other information considered relevant by the HCP • Specific questions requested by the birth defect evaluator

HCP = healthcare provider.

19.5. Attempts to obtain follow-up information

In the month that the follow-up is due, the HCP will be contacted and asked to provide follow-up information. If needed, 3 subsequent attempts will be made approximately every 2 weeks via various modes of communication (eg, phone, fax, e-mail, hardcopy mail). If no response is received from the HCP, additional attempts may occur at the next planned data collection timepoint. When appropriate, the participant will be asked to encourage their HCP

to provide the missing data. After the 3 subsequent attempts, a final communication to obtain follow-up data will be sent to the HCP via certified mail indicating that the participant will be considered lost to follow-up if no further data are received. If, at any point in the follow-up process, the participant withdraws consent or the HCP indicates that the participant is lost to follow-up, no further attempts will be made. The reason the participant was lost to follow-up (eg, no response from HCP, no response from participant, or participant withdrawal of consent) will be documented.

19.6. Follow-up process for clarification of information

For critical data points (eg, EDD, exposure, and outcome data), if there are outstanding questions, discrepancies between forms or missing data, the appropriate HCP will be contacted for clarification. If needed, 3 subsequent attempts will be made at intervals of approximately 2 weeks. If no further information is obtained, qualified registry staff or the principal investigator will make a logical determination on discrepant information based on the available data. All clarifications and/or changes will be documented and traceable.

20. ANNEX 5. LIST OF KNOWN TERATOGENS

This list will be updated over the course of the study as new teratogens are identified.

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	Unknown. Assumed window: first, second, and third trimesters
Oxandrolone	13.3 h	Unknown. Assumed window: first, second, and third trimesters
Prasterone	12 h	Unknown. Assumed window: first, second, and third trimesters
Fluoxymesterone	9.2 h	Unknown. Assumed window: first, second, and third trimesters
Angiotensin II receptor antagonists		
Candesartan	9 h	First, second, and third trimesters
Eprosartan	20 h	First, second, and third trimesters
Irbesartan	11 to 15 h	First, second, and third trimesters
Losartan	2 h	First, second, and third trimesters
Olmesartan	13 h	First, second, and third trimesters
Tasosartan	Not available, but half-life of angiotensin II receptor antagonists ranges from 1 to 3 d	First, second, and third trimesters
Telmisartan	24 h	First, second, and third trimesters
Valsartan	6 h	First, second, and third trimesters
Angiotensin-converting enzyme inhibitors		
Benazepril	10 to 11 h	First, second, and third trimesters
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

Drug class/generic name	Half-life	Relevant exposure window
Perindopril	0.8 to 1 h	First, second, and third trimesters
Quinapril	3 h	First, second, and third trimesters
Ramipril	13 to 17 h	First, second, and third trimesters
Trandolapril	6 h	First, second, and third trimesters
Anti-arrhythmics		
Amiodarone	61 d	First, second, and third trimesters
Antibiotics		
Sulfamethoxazole/ Trimethoprim	8 to 10 h	3 months before conception and first trimester for MCMs and second trimester for preterm birth and low birth weight
Anticoagulants		
Acenocoumarol	8 to 11 h	First, second, and third trimesters
Dicumarol	1 to 2 d	At least 2 weeks before conception and first, second, and third trimesters
Phenprocoumon (fenprocoumon)	4 to 6 d	First, second, and third trimesters
Warfarin	40 h	At least 2 weeks before conception and first, second, and third trimesters
Antidepressants		
Paroxetine	21 h	5 days prior to conception, and first trimester
Anti-epileptics		
Trimethadione/ Paramethadione	Paramethadione—12 to 24 h Trimethadione—11 to 16 h	First, second, and third trimesters
Valproic Acid, Valproate	9 to 16 h	Primarily first trimester, but MCMs have been associated with second and third trimester exposures
Carbamazepine	12 to 65 h	First, second, and third trimesters
Ethotoin	3 to 9 h	First, second, and third trimesters
Phenytoin, Fosphenytoin	Phenytoin: 7 to 42 h Fosphenytoin: 15 min	First, second, and third trimesters
Primidone	10 h	First, second, and third trimesters
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	Unknown. Assumed window: first, second, and third trimesters

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

Drug class/generic name	Half-life	Relevant exposure window
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	12 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
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

Drug class/generic name	Half-life	Relevant exposure window
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
Mitocycine	46 min	6 months before conception and first, second, and third trimesters
Mitoxantrone	23 to 215 h	Not in TERIS. Assumed window: first, second, and third trimesters
Nelarabine	Adults: prodrug: 30 min; ara-G: 3 h	Unknown. Assumed window: first, second, and third trimesters
Oxaliplatin	392 h	9 months before conception and first, second, and third trimesters
Paclitaxel	13 to 52 h	6 months before conception and first, second, and third trimesters
Pemetrexed	3.5 h	6 months before conception and first, second, and third trimesters
Pembrolizumab	22 d	4 months before conception and first, second, and third trimesters
Pentostatin	5.7 h	Not in TERIS. Assumed window: first, second, and third trimesters
Procarbazine	IV, approximately 10 min	Not in TERIS. Assumed window: first, second, and third trimesters
Raltitrexed	260 h	6 months before conception and first, second, and third trimesters

Drug class/generic name	Half-life	Relevant exposure window
Sorafenib	25 to 48 h	6 months before conception and first, second, and third trimesters
Streptozocine	Systemic: 35 min unchanged drug; 40 h metabolites	6 months before conception and first, second, and third trimesters
Sunitinib	40 to 60 h	1 month before conception and first, second, and third trimesters
Tegafur	6.7 to 11.3 h	6 months before conception and first, second, and third trimesters
Temozolomide	1.8 h	6 months before conception and first, second, and third trimesters
Teniposide	5 h	Not in TERIS. Assumed window: first, second, and third trimesters
Thioguanine	80 min	Not in TERIS. Assumed window: first, second, and third trimesters
Thiotepa	1.4 to 3.7 h	6 months before conception and first, second, and third trimesters
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
Endothelin receptor antagonists		
Ambrisentan	15 h	Unknown. Assumed window: First, second, and third trimesters
Bosentan	5 to 8 h	2 days prior to conception and 1st trimester
Macitentan	16 to 48 h	Unknown. Assumed window: First, second, and third trimesters
Estrogens		

Drug class/generic name	Half-life	Relevant exposure window
Diethylstilbestrol	Diethylstilbestrol reaches peak concentration within 20 to 40 min, having a primary half-life of 3 to 6 h. It has a terminal half-life of 2 to 3 d due to entero-hepatic circulation	First, second, and third trimesters
Immunomodulatory agents		
Mycophenolate mofetil	16 h	First, second, and third trimesters
Thalidomide	5 to 7 h	1 month before conception and first, second, and third trimesters
Penicillamine	2 to 4 h	First, second, and third trimesters
Azathioprine	5 h	Primarily first trimester, but other outcomes have been associated with exposures “during pregnancy”
Leflunomide	432 to 456 h	2 years before conception and first, second, and third trimesters
Mycophenolic acid	8 to 16 h	Primarily first trimester, but other outcomes have been associated with exposures “during pregnancy”
Lenalidomide	3h	Unknown. Assumed window: first, second, and third trimesters
Pomalidomide	7.5 to 9.5 h	Unknown. Assumed window: first, second, and third trimesters
Mood stabilizer		
Lithium	24 h	First, second, and third trimesters
Nonsteroidal anti-inflammatory drugs		
Aspirin	30 h	Second and third trimesters; unlikely risk associated with first trimester exp
Ibuprofen	2.2 h	Second and third trimesters; unlikely risk associated with first trimester exp
Indomethacin	4.5 h	Second and third trimesters; unlikely risk associated with first trimester exp
Naproxen	17 h1	Second and third trimesters; unlikely risk associated with first trimester exp
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

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

Drug class/generic name	Half-life	Relevant exposure window
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
Other		
Methylene blue	24 h	5 days prior to conception, and first, second, and third trimesters
Riociguat	12 h	Unknown. Assumed window: first, second, and third trimesters
Sparsentan	9.6 h	Unknown. Assumed window: first, second, and third trimesters

ara-G = arabinosyl guanine; IV = intravenous; MCM = major congenital malformation; TERIS = Teratogen Information System.

Sources: Eltonsy et al. 2016; TERIS 2021; DrugBank online available at https://go.drugbank.com; product labels, which are available at: https://www.accessdata.fda.gov/scripts/cder/daf/ and https://dailymed.nlm.nih.gov/dailymed/index.cfm summary of product characteristics at https://www.ema.europa.eu/en/medicines and https://products.mhra.gov.uk/, product monographs at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.