NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Observational Cohort Study of Zavegepant Safety in Pregnancy within a US Claims Database
Protocol number	C5301027
Protocol version identifier	Version 3.0
Date	24 October 2024
EU Post Authorization Study (PAS) register number	Study will be registered prior to the start of data collection
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 compared to individuals with migraine unexposed to zavegepant in pregnancy? Primary objectives: 1. To estimate the prevalence of major congenital malformation (MCM) births among pregnant individuals with migraine who are (1) exposed to zavegepant (exposed cohort), (2) unexposed to zavegepant (treated comparator cohort), and (3) unexposed to migraine treatment (untreated comparator cohort). 2. To estimate the relative risk of MCM births in the exposed cohort versus the comparator cohorts, if sample size permits. Secondary objectives: 1. To estimate the prevalence of the following secondary outcomes in the 3 study cohorts: spontaneous abortions, pregnancy complications (pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension), stillbirths, preterm births, and small for gestational age (SGA) births. 2. To estimate the relative risk of each of the secondary outcomes in the exposed cohort versus the comparator cohorts, if sample size permits.

Country of study	United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACOG	American College of Obstetricians and Gynecologists
AE(M)	Adverse event (monitoring)
ASA	Acetyl-salicylic acid
ATT	Average treatment effect among the treated
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CGRP	Calcitonin gene-related peptide
CI	Confidence interval
CKD	Chronic kidney disease
CMV	Cytomegalovirus
CPT®	Current Procedural Terminology
DAPI	Optum Dynamic Assessment of Pregnancies and Infants
DCT	Data collection tool
ED	Emergency department
EDC	Estimated date of conception
EUROCAT	European Surveillance of Congenital Anomalies programme
FDA	US Food and Drug Administration
GPP	ISPE Guidelines for Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
IEC	Independent ethics committee
IP	Inpatient
IPTW	Inverse probability of treatment weights
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
LASSO	Least absolute shrinkage and selection operator
LMP	First day of last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
NDC	National drug code
NI(S)	Non-interventional (study)
NSAID	Non-steroidal anti-inflammatory drug
OP	Outpatient
ORD	Optum Research Database
PA(S)S	Post-authorization (safety) study
PMR	Post-marketing requirement
PPV	Positive predictive value
SAP	Statistical analysis plan
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SAS	Statistical Analysis Software
SGA	Small for gestational age
SOP	Standard Operating Procedure
TERIS	Teratogen information system
TORCH	Toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, herpes simplex, and Zika virus disease
US	United States
YRR	Your Reporting Responsibilities

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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4. ABSTRACT

Title: Observational Cohort Study of Zavegepant Safety in Pregnancy within a US Claims Database

Version 3.0, 24 October 2024

Authors: Monica Bertoia, Pfizer Inc.; Rachel Ogilvie, Optum Epidemiology; Jessica Franklin, Optum Epidemiology.

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. There is limited data on the safety of zavegepant when used during pregnancy. This non-interventional study is designated as a post-authorization safety study (PASS) and 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 compared to individuals with migraine unexposed to zavegepant in pregnancy?

Primary objectives:

1. To estimate the prevalence of major congenital malformation (MCM) births among pregnant individuals with migraine who are (1) exposed to zavegepant (exposed cohort), (2) unexposed to zavegepant (treated comparator cohort), and (3) unexposed to migraine treatment (untreated comparator cohort).
2. To estimate the relative risk of MCM births in the exposed cohort versus the comparator cohorts, if sample size permits.

Secondary objectives:

1. To estimate the prevalence of the following secondary outcomes in the 3 study cohorts: spontaneous abortions, pregnancy complications (pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension), stillbirths, preterm births, and small for gestational age (SGA) births.

2. To estimate the relative risk of each of the secondary outcomes in the exposed cohort versus the comparator cohorts, if sample size permits.

Study design: Observational cohort study within a US-based health insurance claims database. Three study cohorts will be identified among individuals with migraine: pregnancies exposed to zavegepant and 2 propensity score-matched (1:3) comparator groups of pregnancies exposed to other migraine therapies and unexposed to migraine therapies, respectively. A fourth 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.

Population: Pregnancies among individuals with migraine with an estimated date of conception (EDC) between 09 March 2023 and 31 December 2030 (or most recent data available at the time of the last data extract).

Variables: Zavegepant and exposure to other migraine treatments will be identified by claims for drug dispensings or administrations. Exposure periods for each medication will be defined using the date of dispensing or administration and the days' supply or recommended administration schedule plus 5 times the half-life of the therapy. The study outcomes will be identified using claims-based algorithms, and the primary outcome (MCM) will be adjudicated via medical records. All covariates will be identified using claims data, including key risk factors for the study outcomes, predictors of treatment choice, and demographics.

Data sources: The Optum Research Database (ORD), containing eligibility, pharmacy claims, and medical claims data from a large US health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US and include 12.0 million individuals with both medical and pharmacy benefit coverage in 2022.

Study size: The target size is 884 zavegepant-exposed pregnancies and 2,652 pregnancies in each comparator group, which will provide an estimated 80% power to detect an MCM relative risk of 2.0 or greater.

Data analysis: Interim reports will include counts of pregnancies meeting the eligibility criteria for the study cohorts, cohort characteristics, and outcome counts. The final report will include a description of the study cohorts, prevalence of the study outcomes by cohort, a propensity score-matched comparative analysis that estimates the relative risk of adjudicated MCM, and if sample size permits, a propensity score-matched comparative analysis that estimates the relative risks of the secondary outcomes.

Milestones: The planned milestones for submission to the FDA are the draft protocol in November 2023, the final protocol in June 2024, annual interim reports every June from 2025 to 2030, and the final study report in June 2032 (or earlier if target sample size is achieved).

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (Substantial or Administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
V3.0	24 October 2024	Administrative	3	Updated primary Optum Epidemiology author from John Seeger to Jessica Franklin	Administrative update
V3.0	24 October 2024	Substantial	4, 8	Revised primary objectives to include the comparative MCM analysis	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	4, 9.5	Reverted back to original sample size calculations and target accrual that did not account for the proportion of patients that are medical record eligible and the proportion of patients for whom medical records are obtained	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	6.0	Revised end of data collection date to align with planned final data pull	Clarification
V3.0	24 October 2024	Substantial	8.0	Added hypothesis statements for the comparative objectives	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	9.1	Clarified that the cohort entry date and pregnancy start date for each pregnancy will be the EDC, defined as 2 weeks after the estimated LMP	Clarification
V3.0	24 October 2024	Substantial	9.2.2	Clarified that the pregnancies exposed to other CGRP medications will not be included in the primary analysis, but will be included in a sensitivity analysis	Clarification
V3.0	24 October 2024	Substantial	9.2.3, 9.3.2.1	Revised MCM analyses to exclude pregnancies with teratogen exposure within a 5-half-life time window prior to EDC through the end of pregnancy (rather than through the end of the first trimester)	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	9.2.4	Clarified that pregnancies included in the zavegepant-exposed cohort may be exposed to migraine medications other than those used to define the treated comparator group	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	9.2.4, 9.2.5, 9.2.6,	Removed ergots and topiramate from the treated comparator cohort	Methodological update

Version Identifier	Date	Amendment Type (Substantial or Administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
			9.2.10, 9.3.1.2		
V3.0	24 October 2024	Substantial	9.2.10	Clarified that the nonmigraine cohort will exclude pregnancies with a dispensing of zavegepant, triptans, or ditans during outcome-specific exposure windows	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	9.3.1	Clarified that the definition of exposure for migraine medications applies to acute (as needed) and preventive migraine medications, including CGRP medications	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	9.3.1.2	Reorganized comparator treatment list for clarity	Clarification
V3.0	24 October 2024	Substantial	9.3.2	Noted that some secondary outcomes may be adjudicated in the final report if imbalances are observed in interim reports	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	9.3.2	Designated Algorithm B for the preterm birth outcome as the primary algorithm, and algorithms A and C as sensitivity analyses	Methodological update
V3.0	24 October 2024	Substantial	9.3.2.6	Corrected definition of preterm birth from <35 gestational weeks to <37 gestational weeks	Correction
V3.0	24 October 2024	Substantial	9.3.3, Annex 5	Removed gestational diabetes and gestational hypertension from list of covariates because these are now study outcomes	Correction
V3.0	24 October 2024	Substantial	9.7.2.1	Revised from 1 propensity score calculated for each pregnancy to 3: 1 based on exposure in the first trimester, 1 based on exposure within the first 20 gestational weeks, and 1 based on exposure during the full pregnancy period.	FDA 10 October 2024 comments
V3.0	24 October 2024	Substantial	9.7.2.3	Clarified that if propensity score weighting is used instead of matching, propensity scores will be used to calculate IPTW weights for estimation of the average treatment effect among the treated (ATT)	FDA 10 October 2024 comments

Version Identifier	Date	Amendment Type (Substantial or Administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
V3.0	24 October 2024	Substantial	9.7.4.10	Added a quantitative bias analysis using the PPV from MCM adjudication	Clarification
V3.0	24 October 2024	Substantial	Annex 5	Removed repeated drugs	Correction
V2.0	01 June 2024	Administrative	6.0	Noted date of draft protocol submission in milestones table	Administrative update
V2.0	01 June 2024	Administrative	6.0	Revised end of data collection to align with date of final report	Administrative update
V2.0	01 June 2024	Substantial	9.2.6	Added untreated comparator group	FDA 26 April 2024 comments
V2.0	01 June 2024	Substantial	9.3.2	Added gestational diabetes, gestational hypertension, and preterm birth as outcomes	FDA 26 April 2024 comments
V2.0	01 June 2024	Substantial	9.2.8	Changed definition of pregnancy start to EDC rather than last menstrual period (LMP)	FDA 26 April 2024 comments
V2.0	01 June 2024	Substantial	9.2.1	Expanded inclusion criteria to include individuals 15-50 years old (rather than 18-49 years old)	FDA 26 April 2024 comments
V2.0	01 June 2024	Substantial	9.2.2	Updated exclusion criteria to exclude pregnancies with exposure to any CGRP medication (rather than CGRP receptor antagonist)	FDA 26 April 2024 comments
V2.0	01 June 2024	Substantial	9.5	Updated sample size calculation	FDA 26 April 2024 comments
V2.0	01 June 2024	Substantial	9.2,2, 9.2.3, 9.2.4, 9.2.5, 9.2.6, 9.2.10	Updated exposure definitions	FDA 26 April 2024 comments
V2.0	01 June 2024	Substantial	9.7.4.	Edited sensitivity analyses	FDA 26 April 2024 comments

6. MILESTONES

Milestone	Planned date	Actual date
Draft protocol	30 November 2023	29 November 2024
Final protocol	30 June 2024	
Registration in the EU PAS register	Prior to the start of data collection	
Start of data collection *Date for starting data extraction for the purposes of the primary analysis.*	1 January 2025	
Interim report 1	30 June 2025	
Interim report 2	30 June 2026	
Interim report 3	30 June 2027	
Interim report 4	30 June 2028	
Interim report 5	30 June 2029	
Interim report 6	30 June 2030	
End of data collection *Date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).*	1 January 2031[1]	
Final study report *Must be submitted within 12 months of the end of data collection*	30 June 2032	

1. This date refers the date of the final data pull

7. RATIONALE AND BACKGROUND

In March 2023, the United States (US) Food and Drug Administration (FDA) approved zavegepant (ZAVZPRET™ label 2023) for the acute treatment of migraine with or without aura in adults. Zavegepant is the first calcitonin gene-related peptide (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 females, with a prevalence of 21% in US females and 10% in US males (Burch et al. 2018). Prevalence peaks in mid-life, and females 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).

Recommendations for treatment of migraine during pregnancy differ from the general population. The American College of Obstetricians and Gynecologists (ACOG) currently recommends acetaminophen, with or without caffeine, as the initial therapy for treatment of acute migraine during pregnancy (ACOG 2020). Antiemetics such as metoclopramide, in combination with diphenhydramine, are also safe for use for pregnant individuals. Triptans are sometimes used as a second-line therapy, with sumatriptan having the most evidence supporting its use. Nonsteroidal anti-inflammatory drugs (NSAIDs) are only considered safe to use during the second trimester of pregnancy. Butalbital and opioids should not be used during pregnancy, while ergot-derivatives are contraindicated because of their ability to stimulate uterine contractions (ACOG 2020). Ditans and oral CGRPs are not currently recommended for use in pregnancy due to lack of evidence.

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). The purpose of this study is to assess the safety of zavegepant when used in pregnancy in terms of risk of major congenital malformations (MCMs), spontaneous abortions, pregnancy complications (pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension), stillbirths, preterm births, and small for gestational age (SGA) births. This non-interventional study is designated as a post-authorization safety study (PASS) and is a postmarketing 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 compared to individuals with migraine unexposed to zavegepant in pregnancy?

Primary objectives:

1. To estimate the prevalence of MCM births among pregnant individuals with migraine who are (1) exposed to zavegepant (exposed cohort), (2) unexposed to zavegepant (treated comparator cohort), and (3) unexposed to migraine treatment (untreated comparator cohort).

2. To estimate the relative risk of MCM births in the exposed cohort versus the comparator cohorts, if sample size permits.

   Hypothesis: there is no difference in the risk of MCM births between exposed and comparator cohorts (ie, the null hypothesis, or a relative risk of 1.0).

Secondary objectives:

1. To estimate the prevalence of the following secondary outcomes in all 3 study cohorts: spontaneous abortions, pregnancy complications (pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension), stillbirths, preterm births, and SGA births.
2. To estimate the relative risk of each of the secondary outcomes in the exposed cohort versus the comparator cohorts, if sample size permits.

   Hypothesis: there is no difference in the risk of secondary outcomes between exposed and comparator cohorts (ie, the null hypothesis, or a relative risk of 1.0).

9. RESEARCH METHODS

9.1. Study design

This is an observational cohort study using an existing US-based health insurance claims database (containing prospectively collected data). Three study cohorts of pregnancies will be identified among individuals with migraine: a cohort of zavegepant-exposed pregnancies and 2 propensity score-matched (1:3) comparator groups of pregnancies exposed to other migraine therapies and unexposed to migraine therapies, respectively. The cohort entry date (ie, index date) and pregnancy start date for each pregnancy will be the estimated date of conception (EDC), defined as 2 weeks after the estimated first day of the last menstrual period (LMP). The primary outcome is MCM, which will be confirmed via medical record review. The secondary outcomes are spontaneous abortion, pregnancy complications (pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension), stillbirth, preterm birth, and SGA. The primary analysis will calculate outcome prevalence in each study cohort, and the relative risks for MCM comparing zavegepant-exposed pregnancies to propensity score-matched treated comparators and untreated comparators (1:3 matching). If sample size permits, the secondary analysis will calculate relative risks for the secondary outcomes. A fourth 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.

9.2. Setting

The base population will include all pregnancies among individuals with migraine with an EDC between 09 March 2023 and 31 December 2030 (or most recent data available at the time of the last data extract) within the US-based health insurance claims database.

9.2.1. Inclusion criteria

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

1. Age 15-50 years at EDC
    - Per FDA recommendation, age range expanded to include pregnancies among those < 18 years
2. EDC during the study period
3. Continuous health plan enrollment with medical and pharmacy benefits during the 6-month period before and including EDC. This enrollment criteria only applies to the pregnant individual.

9.2.2. Exclusion criteria

Pregnancies meeting any of the following exclusion criteria will not be included in the primary analysis:

1. Exposure to a CGRP receptor antagonist other than zavegepant (ie, rimegepant, ubrogepant, atogepant) or a CGRP monoclonal antibody (ie, erenumab, fremanezumab, galcanezumab, eptinezumab) during pregnancy. Exposure periods for each CGRP medication will be defined for each pregnancy using the date of dispensing or administration and the days' supply or recommended administration schedule plus 5 times the half-life of the therapy. This list may be updated if other CGRP medications are approved during the study period.

Pregnancies exposed to CGRP medications other than zavegepant will be excluded because interpreting the study results and potential safety signals would be challenging given these are similar medications to zavegepant.

A sensitivity analysis (Section 9.7.4.4) will allow for co-exposure to CGRP medications.

9.2.3. Additional exclusion criteria for the study population included in the analysis of MCM

1. Pregnancies with exposure to known teratogens within a 5-half-life time window prior to EDC through the end of pregnancy (Annex 3)
2. Pregnancies with infections known to cause congenital anomalies: TORCH infections (toxoplasmosis, other [syphilis, varicella-zoster, parvovirus B19], rubella, cytomegalovirus, herpes simplex, and Zika virus disease)
3. Infants with syndromic or chromosomal anomalies identified during pregnancy or at birth (ie, Down syndrome, trisomies 18 and 13, and other trisomies; monosomies and deletions from the autosomes; balanced re-arrangements and structural markers; Turner’s syndrome, other sex chromosome abnormalities, and other chromosomal abnormalities)

9.2.4. Zavegepant-exposed cohort

The zavegepant-exposed cohort will include eligible pregnancies that meet the following criteria:

1. ≥ 1 exposure period for zavegepant that overlaps with the relevant exposure window (Table 4). An exposure period for zavegepant will be defined for each pregnancy using the date of dispensing or administration as the start of exposure, and the days' supply or recommended administration schedule plus 5 times the half-life of the therapy as the length of exposure.
2. No exposure period for triptans or ditans that overlaps with the relevant exposure window (Table 4)
3. Migraine, based on the criteria summarized in Table 3

An exposure window that begins 30 days prior to the EDC was selected to reduce misclassification. While some patients dispensed an acute migraine treatment > 30 days prior to EDC may use that treatment during pregnancy, a shorter time window reduces misclassification, as individuals with a recent dispensing are more likely to use the dispensed treatment within 30 days. Based on zavegepant's 6.55-hour half-life and pharmacy coverage limits on the quantity of dispensings, an exposure window beginning 30 days prior to the EDC is appropriate.

Pregnancies included in the zavegepant-exposed cohort may be exposed to migraine medications other than those used to define the treated comparator group.

9.2.5. Treated comparator cohort

The treated comparator cohort will include eligible pregnancies that meet the following criteria:

1. ≥ 1 exposure period for a medication indicated for the acute treatment of migraine that overlaps with the relevant exposure window (Table 4). Exposure periods for migraine medications will be defined for each pregnancy using the date of dispensing or administration as the start of exposure, and the days' supply or recommended administration schedule plus 5 times the half-life of the therapy as the length of exposure.
    a. Triptans and ditans
2. No exposure period for zavegepant that overlaps with the relevant exposure window (Table 4)
3. Migraine, based on the criteria summarized in Table 3

See Annex 2 for a complete list of migraine treatments.

9.2.6. Untreated comparator cohort

The untreated comparator cohort will include eligible pregnancies that meet the following criteria:

1. No exposure periods for zavegepant, triptans, and ditans that overlap with an exposure window (defined as 30 days prior to EDC through the end of the relevant exposure window [Table 4])
2. Migraine, based on the criteria summarized in Table 3

See Annex 2 for a complete list of migraine treatments. Exposure to other chronic or preventive migraine treatments will be allowed and adjusted for in final analyses.

9.2.7. Study period

The study period will begin on 09 March 2023, aligning with the date of FDA approval of zavegepant in the US. The study period will end on 31 December 2030 (or most recent data available at the time of the last data extract), or earlier if target sample size is achieved (see Section 9.5).

9.2.8. Pregnancy identification

Published algorithms will be used to identify pregnancies (Bertoia et al. 2022). Briefly, pregnancies will be identified based on the presence of either International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) Z3A diagnosis codes or pregnancy outcome codes. Z3A codes denote weeks of gestation; for example, Z3A.20 denotes 20 weeks' gestation and Z3A.25 denotes 25 weeks' gestation. Pregnancy outcome codes (eg, delivery, cesarean section, spontaneous abortion) will include ICD-10-CM diagnosis or procedure codes, Current Procedural Terminology (CPT®[1]) codes, and Healthcare Common Procedure Coding System (HCPCS) codes.

The pregnancy start date will be the EDC, defined as 2 weeks after the first day of the last menstrual period (LMP).

Published, validated algorithms will be used to estimate LMP (Chomistek et al. 2023). These algorithms use ICD-10-CM Z3A diagnosis codes denoting weeks of gestation. For example, if the code Z3A.12 (12 weeks gestation) is observed on 26 March 2023, the LMP is estimated as 12 weeks prior or 01 January 2023 (Bertoia et al. 2022). For the small proportion of pregnancies without Z3A codes, a standard gestational length is applied based on the observed outcome (eg, 39 weeks for term livebirths and 28 weeks for stillbirths). In a sample of 157 pregnancies with at least 1 Z3A code, there was a median difference of 4 days

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between the estimated LMP and the adjudicated LMP (Chomistek et al. 2023). When no Z3A codes were present (96% of which were spontaneous abortions), there was a median difference of 16 days between the estimated LMP and adjudicated LMP (n = 48) (Chomistek et al. 2023).

The pregnancy end date will be assigned to the date of the pregnancy outcome (eg, fetal death, livebirth), as described previously (Bertoia et al. 2022). Briefly, diagnosis and procedure codes are used to determine the outcome type and date. If diagnosis codes and procedure codes are observed on the same date, the outcome date is assigned to the earliest date with both types of codes. Otherwise, the outcome date is assigned to the earliest date with a diagnosis code (livebirth, stillbirth) or the earliest date with a procedure code (ectopic pregnancy, molar pregnancy, abortion).

A list of pregnancy dates and definitions can be found in Table 1. Note that while the pregnancy start date and cohort entry date will be the EDC, clinical definitions of pregnancy trimesters are anchored by LMP.

Table 1. Pregnancy dates

Date	Definition
LMP	• First day of last menstrual period • 0 gestational weeks$^{0/7\ days}$
Gestational age	• Weeks of gestation • Anchored by LMP • Number of completed weeks elapsed after LMP
Conception	• Typically estimated as LMP + 2 weeks • 2 gestational weeks$^{0/7\ days}$
First trimester	• Begins at EDC • Ends at 13 weeks$^{6/7\ days}$
Second trimester	• Begins at 14 weeks$^{0/7\ days}$ • Ends on 27 weeks$^{6/7\ days}$
Third trimester	• Begins at 28 weeks$^{0/7\ days}$ • Ends at pregnancy outcome
Pregnancy period	• Begins at date of conception • Ends at pregnancy outcome

Abbreviation: EDC, estimated date of conception; LMP, first day of last menstrual period.

9.2.9. Migraine identification

A modified version of previously published algorithms (Table 2) will be used to identify migraine. The algorithm will require individuals to meet at least 1 of the following criteria, as described in Table 3: 2 treatment dispensings, 2 outpatient or emergency department diagnosis codes, 1 outpatient or emergency department diagnosis code plus 1 treatment dispensing, 1 inpatient diagnosis code plus 1 treatment dispensing, or 1 outpatient or emergency department diagnosis code plus 1 inpatient diagnosis code.

This algorithm is similar to those published by Hoffman et al. (2019) and Yusef et al. (2018), incorporating ICD codes and migraine-specific medications. However, it uses ICD-10-CM rather than ICD-9-CM diagnosis codes. It is generally aligned with the algorithm proposed by Wood et al. (2021) but with a broader time interval for code identification (any time

before or during pregnancy versus in the 90 days before LMP). The time interval was relaxed based on the significant under-ascertainment of migraine in claims data observed by Kolodner et al. (2004) and the chronic nature of the disease.

Kolodner et al. (2004) observed a specificity of 99% for a migraine diagnosis and 90-99% for various migraine treatments (class I-V) among 1,766 female patients enrolled in a managed care organization who completed a telephone interview. Sensitivity was lower: a migraine diagnosis code was associated with a sensitivity of 19% and a class I-V migraine treatment was associated with a sensitivity of 3-20%.

During the study period, published literature will be searched for a validated ICD-10 claims-based algorithm to identify migraine. If a validated algorithm using ICD-10 codes is found that has suitable performance characteristics, the methods for identifying migraine may be modified. Conversely, if a newly published study indicates the current protocol-specified algorithm has questionable performance characteristics, a validation study may be conducted to determine its performance characteristics.

Table 2. Selected published migraine algorithms

Author, Year, Database	Algorithm	Comments
Yusef et al. 2018 Marketscan	≥ 1 of the following: • 1 medical claim with a migraine diagnosis (ICD-9-CM 346.xx, in any position) associated with an IP stay • 1 medical claim with a migraine diagnosis associated with a neurologist visit • 2 medical claims with a migraine diagnosis associated with an OP physician or ED visit 7-180 days apart • 1 medical claim with a migraine diagnosis associated with an OP physician visit or ED visit **AND** 1 claim for a dispensing/administration of a migraine-specific acute treatment 7-180 days apart • 2 claims for a dispensing/administration of a migraine-specific acute treatment 7-180 days apart	Prevalence of migraine not reported. Assessed in pregnant population. Not validated.

Table 2. Selected published migraine algorithms

Author, Year, Database	Algorithm	Comments

Hoffman et al. 2019
 	
Optum Research Database
	≥ 1 of the following:
	• ≥ 1 IP medical claim with a migraine diagnosis (ICD-9-CM 346.xx) AND 1 of the following, 7-180 days apart:
	  ○ ≥ 1 OP or ED medical claim with a migraine diagnosis
	  ○ ≥ 1 claim for a dispensing/administration of a triptan or ergotamine
	• ≥ 2 OP or ED claims for migraine, 7-180 days apart
	• ≥ 1 OP or ED claims for migraine and 1 or more dispensings for acute migraine-specific treatments, 7-180 days apart
	• ≥ 2 dispensings for acute migraine-specific treatments, 7-180 days apart
	• ≥ 1 claim for migraine and a visit to a neurologist
	(Excluded if epilepsy diagnosis)
		Identified one third of the general population as having migraine.
		
		Not assessed in pregnant population.
		
		Not validated.

Wood et al. 2021 Marketscan	≥ 1 of the following: Primary definition: • ≥ 2 ICD-9-CM codes (346.xx) in the 90 days before LMP • ≥ 1 ICD-9-CM codes in the 90 days before LMP plus a filled triptan prescription at any time during the study period • ≥ 1 ICD-9-CM codes in the 90 days before LMP plus a neurology encounter • ≥ 2 ICD-9-CM codes at any time during the study period plus a neurology encounter Secondary definition: ≥ 1 ICD-9-CM codes in the 90 days before LMP	The primary definition resulted in a prevalence of 1%. The secondary definition resulted in a prevalence of 1.3%. Assessed in pregnant population. Not validated.

Abbreviations: ED, emergency department; ICD-9, International Classification of Diseases, Ninth Revision; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IP, inpatient; LMP, first day of last menstrual period; OP, outpatient.

Table 3. Identification of pregnancies with migraine in the present study

Algorithm Element	Description
Migraine codes	ICD-10-CM: G43.xx (any code nested in G43) in the primary or another position
Migraine-specific treatments	Triptans, ergots, gepants, ditans, CGRP monoclonal antibodies
Period to identify migraine codes and migraine-specific treatments	Any time before or during pregnancy (ie, using data available during the pregnancy [EDC through pregnancy end], during the 6-month minimum continuous enrollment period prior to EDC, and in any available data >6 months prior to EDC)

Table 3. Identification of pregnancies with migraine in the present study

Algorithm criteria
≥ 1 of the following: • ≥ 1 IP claim for migraine AND ≥ 1 OP/ED claim for migraine at least 7 days apart within 1 year • ≥ 1 IP claim for migraine AND ≥ 1 migraine-specific treatment dispensing ≥ 7 days apart within 1 year • ≥ 2 OP/ED claims for migraine ≥ 7 days apart • ≥ 1 OP/ED claim for migraine AND ≥ 1 migraine-specific treatment dispensing ≥ 7 days apart • ≥ 2 migraine-specific treatment dispensings ≥ 7 days apart

Abbreviations: CGRP, calcitonin gene–related peptide; ED, emergency department; EDC, estimated date of conception; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IP, inpatient; OP, outpatient.

9.2.10. Nonmigraine cohort

A fourth, supplemental cohort will be identified to estimate background rates of the study outcomes among pregnant individuals without migraine. The nonmigraine cohort will include pregnancies in individuals without migraine. Each pregnant individual will need to fulfill the following inclusion criteria:

1. Age 15-50 years at EDC
2. EDC during the study period
3. No migraine diagnosis that meets the criteria summarized in Table 3 (any time before the EDC or during pregnancy)
4. No dispensing of zavegepant, triptans, or ditans during the outcome-specific exposure windows found in Table 4
5. Continuous health plan enrollment with medical and pharmacy benefits during the 6-month period before and including EDC

The criteria used to identify the nonmigraine cohort are purposefully broad. This allows for the flexibility to identify strata/subgroups of pregnancies if needed. For example, a subgroup that is similar in terms of age and comorbidities to pregnancies enrolled in the zavegepant pregnancy registry study (C5301026) could be identified.

9.2.11. Cohort entry date

The cohort entry date for each pregnancy will be the EDC.

9.2.12. Baseline period

There is no general baseline period for these analyses. Instead, a specific time window is defined for each of the relevant study variables (Annex 5).

9.2.13. Follow-up

Pregnancy outcomes will be identified from EDC through the earliest of disenrollment from the health plan, the end of the study period, or 42 days post-pregnancy end date. Each infant

will be followed from birth to 12 months of age, or the earliest of death, disenrollment from the health plan, or the end of the study period.

9.3. Variables

Claims will be the data source for most study variables with the following exceptions. First, the primary outcome MCM will include the subset of claims-identified MCM cases that are physician-adjudicated (Section 9.3.2.2). Second, the covariate race/ethnicity will be self-reported (Section 9.3.3).

9.3.1. Exposures

In the exposed and comparator cohorts, exposure periods for migraine medications will be defined for each pregnancy using the date of dispensing or administration as the start of exposure and the days' supply or recommended administration schedule plus 5 times the half-life of the therapy as the length of exposure. This definition applies to acute (as needed) and preventive migraine medications, including CGRP medications. If an exposure period for a migraine medication overlaps with an exposure window, the pregnancy will be considered exposed. The defined exposure window will vary by study outcome, according to its relevant etiologic period (Table 4).

Table 4. Timing of exposure assessment

Outcome	Timing of exposure assessment (relevant etiologic period)
MCM	30 days prior to EDC through end of the first trimester
Spontaneous abortion	30 days prior to EDC through 20 weeks' gestation
Pre-eclampsia	30 days prior to EDC through date of pre-eclampsia
Eclampsia	30 days prior to EDC through date of eclampsia
Gestational diabetes	30 days prior to EDC through date of gestational diabetes
Gestational hypertension	30 days prior to EDC through date of gestational hypertension
Stillbirth	30 days prior to EDC through end of pregnancy
Preterm birth	30 days prior to EDC through end of pregnancy
SGA	30 days prior to EDC through end of pregnancy

Abbreviations: MCM, major congenital malformation; SGA, small for gestational age birth.

9.3.1.1. Zavegepant

Zavegepant dispensings will be identified by National Drug Codes (NDC). The list of NDCs used to identify zavegepant (or ZAVZPRET™) will be updated annually, prior to each data pull.

9.3.1.2. Comparator migraine treatments

The acute migraine treatments used to identify the treated comparator cohort are listed in Table 5. These include treatments specifically indicated or commonly used for migraine. The list of treatments will be updated annually, prior to each data pull.

Table 5. Comparator migraine treatments

Triptans	Almotriptan Eletriptan Frovatriptan Naratriptan Rizatriptan Sumatriptan Zolmitriptan
Ditans	Lasmiditan

9.3.2. Outcomes

The primary outcome is MCM. The secondary outcomes are spontaneous abortion, pregnancy complications (pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension), stillbirth, preterm birth, and SGA. The study outcomes will be identified by ICD-10-CM diagnosis and procedure codes, CPT®[2] procedure codes, and HCPCS procedure codes on claims. All outcomes will be identified via claims-based algorithms and MCM will be adjudicated via medical records. Some secondary outcomes may be adjudicated in the final report if imbalances are observed in interim reports. Table 6 describes the study algorithms and related algorithms from the literature. Annex 4 includes code lists for all study outcomes.

9.3.2.1. MCM (primary outcome)

MCMs and MCM groupings will be defined according to the Metropolitan Atlanta Congenital Defects Program (MACDP) classification for the annual interim and final study analyses (Correa-Villaseñor et al. 2003, Scheuerle and Tilson 2002). In addition, MCMs will be defined based on guidelines from the European Surveillance of Congenital Anomalies programme (EUROCAT) for the final analysis (EUROCAT 2022). If sample size permits, categories of MCM (eg, cardiovascular) and specific malformations (eg, hypospadias, cleft lip) will be explored.

Given no high-performing claims-based algorithm exists for MCM (Chomistek et al. 2023), the final report will use a highly sensitive claims-based algorithm to identify potential cases for medical record validation (Table 6). The algorithm is highly sensitive because it requires only 1 MCM code and is associated with a high proportion of false positives (PPV 44%; Chomistek et al. 2023). This highly sensitive algorithm used to identify all potential cases combined with medical record validation to narrow down to the subset of confirmed cases will result in a highly sensitive and specific definition of MCM. A sensitive and specific algorithm will be used for annual interim reports (Table 6). Although it will not be used for medical record retrieval, the specific algorithm will be included in the final report to facilitate comparisons between interim and final results. Hence, the interim and final reports will include results from both the sensitive and specific algorithms.

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Among others, the outcome definition of MCMs will include:

- Critical congenital cardiac anomalies (ie, cyanotic defects as well as hypoplastic left heart syndrome and pulmonary atresia).
- Transient cardiac defects in term infants (ie, patent foramen ovale, ventricular septal defect, and persistent ductus arteriosus). Certain transient defects may be associated with maternal medication exposure in pregnancy and can vary by age of detection and/or age of resolution (Reller et al. 2008).

The outcome definition of MCMs will exclude:

- Transient cardiac defects in preterm births. These malformations are often physiologically expected in preterm births and/or are found as a result of improved technology and have little clinical significance for most cases.
- Prematurity-related anomalies (eg, patent ductus arteriosus, undescended testes in infants delivered at < 37 gestational weeks) and positional birth defects (eg, torticollis, hip dislocation in infant in breech position).
- Infants with identified syndromic or chromosomal anomalies (ie, Down syndrome; trisomies 18 and 13, and other trisomies; monosomies and deletions from the autosomes; balanced re-arrangements and structural markers; Turner's syndrome, other sex chromosome abnormalities, and other chromosomal abnormalities) (Section 9.2.3).
- Pregnancies exposed to medications with known teratogenic risk within a 5-half-life time window prior to the EDC through the end of the pregnancy (Section 9.2.3).
- Pregnancies and linked infants with exposure to infections known to cause malformations (Section 9.2.3).

The main analysis will evaluate MCMs among liveborn infants linked to their mothers, using codes from the infant's claims and infant medical records for validation. A sensitivity analysis will evaluate MCM in fetuses/infants from all pregnancies, including spontaneous abortions, elective/therapeutic terminations, stillbirths, livebirths without a linked infant record, and livebirths with a linked infant. This sensitivity analysis will use codes from the mother's record.

As noted in Section 9.2.13, infants will be followed until 12 months of age. Previous work in Optum DAPI observed that most congenital malformations were diagnosed within 1 month of birth, although the timing varied by type of malformation (Hughes et al. 2021). Hence, follow-up to 12 months of age is expected to adequately capture MCMs.

9.3.2.2. Medical record validation of MCM

Medical records will be sought for each potential MCM case after accrual of sufficient sample size and prior to the final, comparative analysis. Each case will be physician-adjudicated, and the final analysis will include physician-confirmed cases only. MCM medical record validation will be conducted in zavegepant, treated comparator, and untreated comparator cohorts but not in the nonmigraine cohort.

Medical record retrieval will begin with a review of the chronological listing of relevant claims for each potential case to identify the primary and alternate provider (eg, obstetrician,

pediatrician) mostly likely to yield medical records with the necessary information to confirm case status. Medical records will be sought for all potential cases with at least 1 identified provider. Optum, in collaboration with a physician(s), will develop a medical record review form that includes the clinical elements necessary to confirm the case. Physicians will be asked to send all available medical information occurring during the period of interest (ie, surrounding the service date of the relevant claim). This will include, but is not limited to, the following types of information:

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

For each potential case, 1 medical record will be requested from 1 provider. If a medical record cannot be obtained from this provider, Optum will contact the alternate provider(s). Of those that are requested, approximately 70-85% of the medical records are expected to be successfully obtained (Johannes et al. 2007, Seeger et al. 2006).

The physician adjudicators (blinded to the maternal use/receipt of migraine treatments) will review the medical record for each potential case and adjudicate the MCM. The physician adjudicators will have relevant clinical expertise for MCM adjudication. Each record will be independently adjudicated by 2 physicians, and consensus will be sought for any discrepancies in adjudication results between the physicians. Optum will work with the contracted physicians to achieve consensus, and a third independent physician adjudicator, also with relevant experience for MCM adjudication, will be available to arbitrate remaining discrepancies or break ties in adjudication results, if needed.

9.3.2.3. Spontaneous abortion

Spontaneous abortion will be defined as pregnancy loss at < 20 completed weeks of gestation. Ectopic and molar pregnancies will not be considered spontaneous abortions. Spontaneous abortion outcomes will be identified on maternal claims based on diagnosis and/or procedure codes as outlined in Table 11.

9.3.2.4. Pregnancy complications

Pregnancy complications will include pre-eclampsia, eclampsia, gestational diabetes, and gestational hypertension.

- Pre-eclampsia will be defined by ACOG as proteinuria with either 1) systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more after 20 weeks of gestation in a woman with previously normal blood pressure, or 2) systolic blood pressure of 160 mmHg or more or diastolic blood pressure of 110 mmHg; or in the absence of proteinuria, a new-onset hypertension with thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or

unexplained new headaches unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms (ACOG 2020).

- Eclampsia will be defined as new-onset hypertensive tonic-clonic, focal, or multifocal seizures during pregnancy (ACOG 2020).
- Gestational diabetes will be defined by ACOG as a positive 50 g 1-hour glucose tolerance test administered between 24 and 28 weeks of pregnancy followed by a positive 100 g 3-hour oral glucose tolerance test (ACOG 2018).
- Gestational hypertension will be defined by ACOG as systolic blood pressure 140 mmHg or more or diastolic blood pressure of 90 mmHg or more after 20 weeks gestation in a woman with previously normal blood pressure (ACOG 2020).

All pregnancy complications will be identified on maternal claims based on ICD-10 diagnosis codes found in Table 11.

9.3.2.5. Stillbirth

Stillbirth will be defined as fetal death at ≥ 20 completed weeks of gestation. It will be identified on maternal claims based on the ICD-10 diagnosis codes found in Table 11.

9.3.2.6. Preterm Birth

Preterm birth will be defined as a live birth occurring at < 37 gestational weeks. It will be identified on maternal and infant claims based on the ICD-10 diagnosis codes found in Table 11.

9.3.2.7. SGA

SGA will be defined as a liveborn infant with birth weight below the 10th percentile for gestational age at birth. It will be identified on maternal and infant claims based on the ICD-10 diagnosis codes found in Table 11.

Table 6. Algorithms for the identification of outcomes

Outcome	Algorithm	Denominator	Window for outcome ascertainment*	Validity (when available)
MCM	Specific algorithm (interim + final reports): ≥ 2 infant MCM dx codes at least 30 days apart Sensitive algorithm (interim + final reports): Primary analysis: ≥ 1 infant MCM dx code Sensitivity analysis: ≥ 1 maternal or infant MCM dx code	Primary analysis: pregnancies with livebirth, with linked infant Sensitivity analysis: pregnancies with livebirth (linked or not linked) or non-livebirth	Primary analysis (livebirths): from birth through 365 days after birth Sensitivity analysis (livebirths and non-livebirths): Non-livebirths: from EDC through 42 days after pregnancy Livebirths: from birth through 365 days after birth	MCM PPV 44% (95% CI 35-53%) based on ≥ 1 infant ICD-10-CM dx code and PPV 68% (95% CI 56-80%) based on ≥ 2 codes at least 30 days apart in Optum DAPI (Chomistek et al. 2023)
Spontaneous abortion	≥ 1 maternal spontaneous abortion dx or px code in pregnancy, as identified within Optum DAPI (Bertoia et al. 2022)	All pregnancies	< 20 completed weeks of gestation	Spontaneous abortion PPV 85% (95% CI 78-91%) based on ≥ 1 maternal ICD-10-CM dx or px code in Optum DAPI (Chomistek et al. 2023)
Pre-eclampsia	≥ 1 maternal pre-eclampsia dx code in pregnancy and up to 42 days after pregnancy end	All pregnancies	Any time during pregnancy and through 42 days after the end of pregnancy	Pre-eclampsia PPV 78% (95% CI 61-95%) based on ≥ 1 maternal ICD-10-CM dx code in Optum DAPI (Chomistek et al. 2023)
Eclampsia	≥ 1 maternal eclampsia dx code in pregnancy and up to 42 days after pregnancy end	All pregnancies	Any time during pregnancy and through 42 days after the end of pregnancy	None available

Table 6. Algorithms for the identification of outcomes

Outcome	Algorithm	Denominator	Window for outcome ascertainment*	Validity (when available)
Gestational diabetes	≥ 2 maternal OP diabetes/gestational diabetes dx codes that occurred on different dates PLUS 1 of the following: A CPT[3] code for a glucose tolerance test during the outcome ascertainment window OR A dx code for gestational diabetes during the outcome ascertainment window plus no antidiabetic drug dispensing or code for pre-gestational diabetes between 365 and 180 days prior to the date of delivery or pregnancy outcome	All pregnancies	Any time during pregnancy and through 42 days after the end of pregnancy	Gestational diabetes PPV 88% (95% CI, 75-95%) using ICD-9 codes (Andrade et al 2011)
Gestational hypertension	≥ 1 maternal gestational hypertension dx code in pregnancy and up to 42 days after pregnancy end	All pregnancies	Any time during pregnancy and through 42 days after the end of pregnancy	None
Stillbirth	≥ 1 maternal stillbirth dx or px code or ≥ 1 livebirth and stillbirth dx or px code in pregnancy, as identified within Optum DAPI (Bertoia et al. 2022)	All pregnancies	≥ 20 completed weeks of gestation	Stillbirth PPV 83% (95% CI 71-91%) based on a maternal dx code indicating gestational age ≥ 20 weeks and either ≥ 2 stillbirth-related codes or no other pregnancy outcome code recorded in the US Sentinel System (Andrade et al. 2021)

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Table 6. Algorithms for the identification of outcomes

Outcome	Algorithm	Denominator	Window for outcome ascertainment*	Validity (when available)
Preterm birth	Algorithm A (Sensitivity): ≥ 1 maternal or infant dx code for preterm birth, low birth weight, or specific conditions more common in preterm infants Algorithm B (Primary): ≥ 1 maternal or infant dx code for gestational age in weeks corresponding to < 37 weeks at birth Algorithm C (Sensitivity): Meets criteria for either Algorithm A or Algorithm B	Pregnancies with live birth	< 37 completed weeks of gestation Algorithm A (Sensitivity): within 0-30 days after pregnancy end date Algorithm B (Primary): Maternal codes must be within 0-7 days before pregnancy end; infant codes must be within 0-30 days after pregnancy end date	Algorithm A is adapted from a published algorithm that included only codes designated for use in infants (Eworuke et al., 2012). This algorithm showed a high PPV (> 80% for gestational age at birth of < 34 weeks) in 2 US claims databases. For the present study, the ICD-9 codes in that algorithm will be mapped to ICD-10-CM codes ICD-10-CM maternal codes for preterm delivery will also be included in this study because their ICD-9-CM equivalents have been validated in the US, with PPV of 92% (95% CI, 87%-98%) in infants' claims data and 76% (95% CI, 64%-88%) in mothers' claims (Andrade et al., 2013)
SGA	≥ 1 maternal or infant SGA dx code from delivery to delivery + 30 days	Pregnancies with livebirth, with linked infant	From date of delivery through 30 days after delivery	SGA PPV 92% (95% CI 82-97%) based on ≥ 1 maternal or infant ICD-9-CM dx code recorded in IP or other therapy claims from delivery to delivery + 30 days (He et al. 2020)

*Outcome ascertainment windows may be broadened to allow for capture of codes slightly outside the clinical outcome window, to allow for imprecision in estimating the date of conception. The window for outcome ascertainment will also end at disenrollment or end of the study period.
Abbreviations: CI, confidence interval; DAPI, Dynamic Assessment of Pregnancies and Infants; dx, diagnosis; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; IP, inpatient; MCM, major congenital malformation; OP, outpatient; PPV, positive predictive value; px, procedure; SGA, small for gestational age; US, United States.

9.3.3. Covariates

With the exception of race/ethnicity, information on covariates will be derived from the mother's claims during pregnancy and in all available data prior to the EDC (during continuous enrollment in her health insurance plan). Race/ethnicity will be self-reported.

A list of covariates is provided below, including demographics, risk factors for the study outcomes, and variables associated with migraine treatment choice (ie, potential confounders). Operational definitions, periods of ascertainment, and code lists are described in detail in Annex 5.

Demographic and general characteristics:

- Age at EDC
- Race/ethnicity
- Duration of continuous health plan enrollment before pregnancy
- Calendar year of EDC
- Calendar year of end of pregnancy
- Geographic region (Northeast, West, Midwest, South, unknown)

History of medical conditions:

- Depression or bipolar disorder
- Anxiety or panic disorders (generalized anxiety disorder, panic disorder with and without agoraphobia, social anxiety disorder)
- Obsessive-compulsive disorder
- Schizophrenia
- Epilepsy and seizures
- Alcohol misuse
- Drug misuse
- Hyperlipidemia
- Diabetes
- Hypertension
- Malignancy
- Thyroid disease
- Respiratory disease, including asthma
- Liver disease
- Chronic kidney disease
- Obesity
- Smoking
- History of cardiovascular diseases (myocardial infarction, transient ischemic attack, ischemic stroke, ischemic heart disease, angina, heart failure, cardiac arrhythmia, hemorrhagic stroke, peripheral vascular disease)
- Pain conditions (eg, rheumatoid arthritis, gout)
- Cluster headache

Migraine type (see Annex 5 for operational definitions):

- With or without aura
- With or without intractable pain

Prior obstetric history:

- Gravidity, the number of pregnancies before the current pregnancy
- Parity, the number of vaginal deliveries or C-sections before the current pregnancy
- Spontaneous abortions

- Pregnancy terminations
- Preterm births
- MCMs
- Stillbirths
- SGA births
- Gestational diabetes
- Gestational hypertension

Medications:

- Medications of known teratogenic potential (Annex 3)
- Prescription cannabinoids
- Preventive cluster headache drugs
- Acute cluster headache drugs
- Antidepressants
- Antipsychotics
- Oral antidiabetics
- Insulin
- Antihypertensive medications: calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin II antagonists
- Lipid-lowering drugs
- Antithyroid medications
- Antiplatelet agents
- Anticoagulants
- Anti-emetics and antinauseants
- Other medications associated with the medical conditions identified

Use of preventive migraine drugs (Annex 2):

- Topiramate
- Other anti-epileptics
- Beta-blockers
- Tricyclic antidepressants
- Selective serotonin reuptake inhibitors
- Serotonin-norepinephrine reuptake inhibitors
- Botulinum toxin

Use of acute migraine drugs (Annex 2):

- Triptans
- Ergotamine derivatives
- Prescription NSAIDs
- Aspirin
- Acetaminophen
- Opioids

Health care utilization:

- Number of office visits
- Number of telemedicine encounters

- Number of emergency department visits
- Number of hospitalizations

Characteristics of the current pregnancy:

- Multiple pregnancy
- TORCH infections during pregnancy
- SARS-CoV-2 infection during pregnancy

9.4. Data sources

9.4.1. The Optum Research Database (ORD)

The patients included in this study will be drawn from the ORD, a proprietary research database containing eligibility, pharmacy claims, and medical claims data from a large US health plan affiliated with Optum. The individuals covered by this health plan are geographically diverse across the US. As early as 1993, medical and pharmacy claims data are available for 70 million individuals with both medical and pharmacy benefit coverage. For 2021, data are available for approximately 12.6 million individuals with medical and pharmacy coverage. Optum Epidemiology research activities utilize de-identified data from the research database. In limited instances, patient identifiers may be accessed where applicable law allows the use of patient-identifiable data, and when the study obtains appropriate approvals for accessing data that are not de-identified.

The data include demographics, details from pharmacy claims (reflecting dispensings), all medical and facility claims, including information on the types of services or procedures, and their accompanying diagnoses. The coding of medical claims conforms to insurance industry standards, including:

- Use of designated claims forms (eg, physicians use the Centers for Medicare & Medicaid Services [CMS]-1500 format and hospitals use the universal billing [UB]-04 format)
- ICD-10 diagnosis codes and procedure codes
- CPT®[4] codes
- CMS HCPCS codes

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

- NDC
- Drug name
- Dosage form
- Drug strength
- Fill date
- Days' supply
- Cost information

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- De-identified patient and prescriber codes

The machine-readable dataset of the ORD can be augmented on an ad hoc basis by further inquiry, including medical record review. Approximately 40-50% of patients in the database are eligible for medical record review. The data are only re-identified following approval by an Institutional Review Board (IRB), and all data access conforms to applicable Health Insurance Portability and Accountability Act policies.

9.4.2. The Optum Dynamic Assessment of Pregnancies and Infants (DAPI)

This study will employ DAPI, a proprietary process that includes a set of capabilities and established algorithms that is applied to the ORD claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link mothers' and infants' data in an ongoing manner (Bertoia et al. 2022). The algorithms are based on a combination of validated algorithms as reported in the literature and clinical input. A pregnancy outcome-specific minimum number of weeks between pregnancy outcomes is applied to identify distinct pregnancy episodes within a woman. Mother and infant records are linked through the presence of a common unique family insurance ID. 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, claim(s) relating to the delivery must be within 7 days of the infant's birthdate (or 32 days for multiples).

In comparison with the broader US population, the females of child-bearing age who are included in the ORD (and DAPI) tend to be healthier, reflecting the underlying population of the commercial insurance enrollees, and likely have an age distribution more skewed toward older age, reflecting the age distribution of females within the work force.

Historically, there are approximately 200,000 pregnancies identified each year within the database, of which 80% (with observed outcomes) result in livebirths, 85% of which can be linked to an infant within the database. 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, Carman et al. 2017, Wyszynski et al. 2016).

The fraction of identified deliveries that cannot be matched to an infant is likely due to the infant being covered under a different health insurance plan from the mother. This may occur if the infant were to be added to the other parent's plan (rather than the mother's), if the parents were to switch from individual plans to a family health plan, or if the mother were covered under her parent's policy (in which case a separate plan would need to be purchased for the infant).

For a subset of mothers and infants, Optum can (with appropriate approvals) access medical records.

9.4.3. Medical records

As noted in Section 9.3.2.2, medical records will be sought for the adjudication of the primary outcome MCM. Medical records will not be sought for any other outcome.

9.4.4. Multiple research partners

Optum has extensive experience as both a participating research partner and as the coordinating center for multi-partner studies, including pregnancy studies performed for regulatory purposes. The potential for small numbers of zavegepant-exposed pregnancies may mean that multiple research partners are required to achieve adequate sample size to provide sufficient statistical power for analyses of the less common outcomes. Accrual of zavegepant-exposed pregnancies will be assessed following the third annual interim report, at which point the addition of research partners will be considered.

9.5. Study size

Table 7 presents the number of pregnancies required for a comparative analysis of each of the study outcomes, by true population relative risk, assuming a ratio of 1:3 exposed to unexposed, 80% power, and alpha = 0.05. For the primary outcome MCM, a study size of 464 pregnancies with linked infants exposed to zavegepant in the first trimester exposure window would provide 80% power to reject the null hypothesis if the true population relative risk was 2.0 or greater.

In Optum DAPI, 76% of pregnancies with a known outcome ended in livebirths, and 84% of livebirth pregnancies were linked to infant records (Bertoia et al, 2022). Conservatively assuming 70% of pregnancies will result in a livebirth, and 75% of infants will link to their mother, an estimated 884 zavegepant-exposed pregnancies would need to be accrued. With a 1:3 ratio of exposed to unexposed, this corresponds to 2,652 pregnancies in each comparator group.

Table 7. Estimated number of zavegepant-exposed pregnancies required

Outcome	Outcome prevalence	True population RR			
		2.0	2.5	3.0	4.0
MCM	3%[a]	464	233	146	77
Spontaneous and therapeutic abortion	16%[b]	70	33	20	9
Pre-eclampsia/eclampsia	4.7%[c]	289	144	90	47
Gestational diabetes	8.3%[d]	154	76	47	24
Gestational hypertension	13%[e]	91	44	27	13
Stillbirth	0.4%[b]	3,620	1,829	1,151	619
Preterm birth	10%[f]	124	61	37	19
SGA	11.1%[g]	110	54	33	16

Abbreviations: MCM, major congenital malformation; RR, relative risk; SGA, small for gestational age
Note: The numbers of zavegepant-exposed subjects represent the number of exposed pregnancies needed for the maternal outcomes (spontaneous abortion, pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension, stillbirth) or the number of mother-infant pairs for livebirth outcomes (MCM, preterm birth, SGA).
Assumptions: 80% power, alpha = 0.05, a ratio of exposed to unexposed subjects of 1:3. Calculations were performed using PS: Power and Sample Size Calculation version 3.1.6, Oct-2018 (Dupont and Plummer 1990).
a CDC 2008.
b Data provided by Optum (Optum Research Database, October 2015 through September 2020).
c Fingar et al. 2006.
d MMWR 2023.
e Bello et al 2021.
f Ferre et al 2016.
g Jensen et al. 2019.

The actual study size will depend on zavegepant uptake in the study data source. Table 8 shows counts of pregnancies with at least 1 diagnosis code for migraine by year. The annual interim reports will assess accrual into the 3 study cohorts and the feasibility of meeting the target study size. If the observed accrual indicates a low likelihood of meeting target study size, a second data partner may be considered.

Table 8. Number of pregnancies with migraine by year in Optum DAPI*

	2018	2019	2020	2021	2022	2023	Total
Pregnant individuals with migraine	8,833	9,695	10,171	10,439	6,441	165	40,346
Pregnant individuals with migraine + CGRP receptor antagonists	0	0	10	67	61	4	138
Pregnant individuals with migraine + ditans	0	0	0	2	1	0	3
Pregnant individuals with migraine + triptans	382	378	371	359	239	7	1,649

Abbreviations: CGRP, calcitonin gene-related peptide; DAPI, dynamic assessment of pregnancies and infants
Note: Final sample size for the study could change depending upon criteria applied during the conduct of the protocol and required approvals.
*Data were extracted in June 2023.

9.6. Data management

All analyses will be conducted using Statistical Analysis System (SAS) version 9.4 (SAS Institute Inc., Cary, North Carolina) and SAS Enterprise Guide 6.1 or later. The data will be extracted from the ORD once per report. The annual interim reports will include the structured ORD data only. The final report will additionally incorporate the medical record adjudication results, as described in Section 9.3.2.2.

The following sections of the protocol (Sections 9.6.1 and 9.6.2) pertain to the data collected for the review of medical charts described in Section 9.3.2.2.

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. In this protocol, the DCT refers to the form used for medical record review.

A DCT is required and should be completed for each included patient for whom outcomes are being adjudicated via medical record review. The completed original DCTs are maintained by Optum and should not be made available in any form to third parties, except for appropriate regulatory authorities, without written permission from Pfizer. Optum shall ensure that the DCTs are securely stored at the study site in encrypted electronic form and will be password-protected to prevent access by unauthorized third parties.

Optum has ultimate responsibility for the collection and reporting of all clinical, safety, and laboratory data entered on the DCTs and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent,

legible, timely (contemporaneous), enduring, and available when required. In order to fulfill this responsibility, Optum will confirm that a completed adjudication entry is provided by the clinical reviewer for each medical record that is obtained and made available to the clinical reviewer for adjudication. The DCTs are completed and submitted by the clinician reviewer(s), with time, date, and name of the clinician reviewer(s) recorded, who by submitting the DCTs attest to their accuracy and completeness. Any corrections to entries made in the DCTs or source documents must be dated, initialed, and explained (if necessary) and all prior entries are maintained for documentation.

The source documents are the hospital or the physician's chart. In these cases, data collected on the DCTs must match those charts.

9.6.2. Record retention

To enable evaluations and/or inspections/audits from regulatory authorities or Pfizer, Optum agrees to keep all study-related records, including sufficient information to link records, (eg, DCTs and hospital records), electronic copies of all DCTs, safety reporting forms, source documents, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by Optum according to local regulations or as specified in the Optum contract, whichever is longer. Optum must ensure that the records continue to be stored securely for so long as they are retained.

If Optum becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified, and study records should be retained under an arrangement acceptable to Pfizer that protects the confidentiality of the records (eg, secure off-site storage). Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless Optum and Pfizer have expressly agreed to a different period of retention via a separate written agreement.

If Pfizer would like the Study Records kept longer than the 15-year retention period, Pfizer will notify Optum prior to the end of the 15-year retention period.

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 Pfizer. 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. An overview of the SAP is presented below.

9.7.1. Annual interim reports

Annual interim reports will describe the flow of pregnancies into the 3 migraine cohorts including the number of accrued pregnancies meeting each of the eligibility criteria. Each study cohort will be described with respect to select covariates (Section 9.3.3). All analyses will be descriptive, including the number of observations, mean, standard deviation, median, interquartile range, and range for all continuous variables and counts and percentages for each binary or categorical variable. The nonmigraine cohort will not be included in the annual interim reports.

Claims-identified outcome counts will be provided to assess whether the prevalence estimates incorporated into the power calculation hold. These counts will include non-adjudicated MCM, as identified using the specific algorithm (Section 9.3.2)

There will be no propensity score matching of the exposed to comparator group pregnancies in the annual interim reports and no comparative analyses. As noted in Section 9.4.4, the addition of research partners will be considered after the third annual interim report, based on observed accrual.

9.7.2. Final report

The comparative analysis in the final report will match exposed and comparator pregnancies on propensity scores to identify the final study cohorts. The nonmigraine cohort will not be matched to exposed pregnancies.

9.7.2.1. Propensity scores

Each pregnancy's propensity score (the probability of receiving zavegepant versus a comparator or no treatment, given membership in the study population and a set of covariates) will be estimated using a logistic regression model with exposure status as the outcome (dependent variable). A total of 6 propensity score models will be generated. Three propensity scores will be calculated for each pregnancy separately at the EDC: 1 based on exposure during the first trimester, 1 based on exposure during the first 20 gestational weeks, and 1 based on exposure during the full pregnancy period. Each of these 3 propensity score models will be generated for the comparison of the zavegepant-exposed cohort versus the treated comparator cohort and for the comparison of the zavegepant-exposed cohort versus the untreated comparator cohort, for a total of 6 models. The covariates listed in Section 9.3.3 will be considered for inclusion in the model as independent (predictor) variables. The propensity score model will only include covariate information from EDC or earlier. Hence, the propensity scores will incorporate characteristics at the start of the pregnancy. In addition to the pre-specified variables in Section 9.3.3, the most common diagnoses, procedures, and medications observed prior to EDC will be evaluated to ensure no important confounders are missed.

If there are too many variables given the number of pregnancies exposed to zavegepant (eg, < 10 exposed pregnancies for every variable in the propensity score model), the number of variables may be reduced using a LASSO model, with careful consideration to ensure no clinically meaningful confounders are dropped. Variables with an estimate of 0 in the LASSO model will be dropped from the propensity score variable list, and a logistic regression model will be run using the remaining variables. For variable pairs that are highly correlated (eg, correlation coefficient > 0.9), 1 may be eliminated.

9.7.2.2. Matching

Each zavegepant-exposed pregnancy will be matched to up to 3 comparator pregnancies on propensity score using greedy matching. Matching will be performed for both comparator groups and all relevant exposure windows. With greedy matching, each exposed pregnancy is matched to comparator pregnancies without replacement, beginning with comparator pregnancies with the same propensity score (at a specified level of precision [eg, number of

digits]). When no matches are available at the specified level of precision, the number of digits is reduced digit-by-digit to a maximum caliper of 0.1.

9.7.2.3. Descriptive analyses

The matched study cohorts will be described with respect to all covariates listed in Section 9.3.3 before and after matching, including absolute standardized differences. The calculated standardized differences will account for the 1:n matching (Austin 2008). If any variable remains unbalanced between study groups after matching (eg, absolute standardized difference > 0.1) it may be included as independent (predictor) variables in the outcome models. The overlap of the distribution of propensity scores in the exposed and unexposed groups before and after matching will be described using density plots.

If several zavegepant-exposed pregnancies are dropped from the final study cohorts because they do not match to at least 1 comparator pregnancy, alternatives to propensity score matching will be considered, such as inverse probability of treatment weighting (IPTW) (Desai & Franklin 2019). If IPTW is used, stabilized weights will be estimated using the propensity score, to estimate the average treatment effect among the treated (ATT), with truncation at the first and 99th percentiles (Hernán & Robbins 2020, Stuart 2010). With ATT, weights are calculated for each exposed pregnancy as 1 and for each comparator pregnancy as the propensity score divided by (1-propensity score). If any variable that is a component of the propensity score remains unbalanced between study groups after weighting (eg, absolute standardized difference > 0.1), that variable may be included as an independent (predictor) variable in the outcome models.

The final report will also include a description of the nonmigraine cohort (all covariates listed in Section 9.3.3) and the number of pregnancies meeting each of the cohort-specific eligibility criteria.

9.7.2.4. Prevalence estimates

Prevalence and 95% confidence intervals (CIs) for each of the study outcomes will be estimated for the matched study cohorts and the nonmigraine cohort. The final analyses will be restricted to confirmed cases for MCM (among the subset of preliminary cases identified by the sensitive algorithm). The denominator for each calculation is described in Table 6. The number of potential MCM cases identified, the number of infant/mother records sought, the number of retrieved records, and the number of confirmed cases will be described.

9.7.2.5. Relative risks

Comparative analyses will be conducted for MCMs, and for secondary outcomes if the study cohorts reach the required minimum sample size. Relative risks and corresponding 95% CIs for each of the study outcomes, comparing the matched zavegepant-exposed pregnancies and comparators, will be calculated using log-binomial regression. For MCM, the relative risks will be calculated using confirmed cases only. No comparative analyses will be conducted using the nonmigraine cohort.

The additional/sensitivity analyses described in Section 9.7.4 will be conducted for the final report only.

9.7.3. Missing data

Exposure, outcome, and covariate information will be derived from codes identified in administrative claims. For example, pregnancies without an NDC code for zavegepant are presumed not to have filled a zavegepant prescription, and pregnancies without a diagnosis code for hypertension are presumed to be normotensive. For such variables derived from the presence (or absence) of codes, there are no missing categories.

9.7.4. Additional analyses

9.7.4.1. Sensitivity analyses to account for exposure misclassification

Alternative exposure windows (eg, assessing exposure in the full pregnancy period for analysis of MCM rather than the first trimester [as specified in Table 4]) may be considered.

If sample size permits, an analysis that defines exposure as 2 or more dispensings/administrations will be conducted. An analysis that defines exposure as 1 or more dispensings after the date of conception will also be conducted, if sample size allows. This dispensing-based sensitivity analysis may be more robust to potential misclassification of the exposure period, particularly for migraine treatments with long half-lives (eg, CGRP receptor antagonists).

9.7.4.2. Sensitivity analysis to account for use of preventive and acute migraine therapy

Some members of the study cohorts may be using preventive migraine treatments in addition to the acute migraine treatments required for inclusion. A sensitivity analysis will restrict the study cohorts to individuals using acute migraine treatments only (ie, not exposed to any preventive migraine treatments during pregnancy). Individuals on preventive treatment may have more severe disease compared to individuals on acute treatment, and migraine severity may be a risk factor for some of the study outcomes.

9.7.4.3. Sensitivity analysis allowing for co-exposure

For the comparative analyses, both the zavegepant-exposed cohort and treated comparator cohort will allow for co-exposure to any study drug (and no other non-cohort defining acute or preventive migraine treatments).

9.7.4.4. Inclusion of pregnancies exposed to CGRP medications

A sensitivity analysis will include pregnancies with CGRP monoclonal antibody or CGRP receptor agonist exposure in the zavegepant-exposed and treated comparator cohorts.

9.7.4.5. Sensitivity analysis restricting to pregnancies with migraine prior to pregnancy

For the comparative analyses, all 3 study cohorts will be restricted to pregnancies with migraine prior to pregnancy (and not during pregnancy), as sample size allows.

9.7.4.6. Sensitivity analysis restricted to singleton births

Given multiples have a higher risk of preterm birth, SGA, and postnatal growth deficiency, a sensitivity analysis will restrict to singleton pregnancies.

9.7.4.7. Age stratification

Advanced maternal age pregnancies (pregnancies among individuals aged 35 years or older) have a greater risk of some of the study outcomes such as spontaneous abortion. A sensitivity analysis will stratify the main study results by maternal age, if sample size permits. Age strata may include 15-17 years, 18-34 years, 35-44 years, and 45-50 years or 15-34 years versus 35 years and older, depending on sample size.

9.7.4.8. Quantitative bias analysis for unmeasured confounding

A quantitative bias analysis will be conducted to assess the degree of unmeasured confounding required to explain the observed relative risks (ie, the 'rule-out' approach). This method allows for a range of reasonable values of the prevalence of the unmeasured confounder and various magnitudes of association with risk of the study outcome (Schneeweiss 2006).

9.7.4.9. Quantitative bias analysis for unobserved MCM

Given some MCMs may result in spontaneous abortions, elective/therapeutic terminations, and stillbirths, a sensitivity analysis will be conducted that makes assumptions about the proportion of each that could be due to MCMs. This quantitative bias analysis will consider a range of proportions and the corresponding effect on the estimated relative risks. For example, 5% of non-livebirths will be considered MCMs, 10%, 20%, etc.

9.7.4.10. Quantitative bias analysis using PPV from MCM adjudication

The primary analysis of MCM will only include clinician-adjudicated cases. However, not all pregnancies are eligible for medical record retrieval, not all sought medical records are received, and not all received medical records contain sufficient information for a clear determination of case status. Therefore, a sensitivity analysis will be performed in which the PPV obtained from adjudicated MCMs will be applied to the claims-based estimates of relative risk.

9.8. Quality control

The conduct and reporting of this study follows Optum Epidemiology's Standard Operating Procedures (SOPs) that are consistent with the International Society for Pharmacoepidemiology (ISPE)'s Guidelines for Good Pharmacoepidemiology Practices (GPP) (ISPE 2015) as well as the FDA's Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/best-practices-conducting-and-reporting-pharmacoepidemiologic-safety-studies-using-electronic) and FDA's Real-World Data: Assessing Electronic Health Records and Medical Claims Data To Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance, September 2021 (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/real-world-data-assessing-electronic-health-records-and-medical-claims-data-support-regulatory). For pregnancy safety studies such as this, the suggested study design and methodology are consistent with the FDA draft guidance document Postapproval Pregnancy Safety Studies Guidance for Industry (https://www.fda.gov/regulatory-information/search-fda-guidance-documents/postapproval-pregnancy-safety-studies-guidance-industry). In

particular, the SOPs in place at Optum prescribe that processes and deliverables are documented, reviewed, and validated in sufficient detail to allow for subsequent re-examination or replication.

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

The validity of the ORD for epidemiologic research (as compared with data abstracted from medical records) has been established (Dore et al., 2011; Eng et al., 2012; Loughlin et al., 2010; Quam et al., 1993).

9.9. Limitations of the research methods

While claims data are extremely valuable for pharmacoepidemiology research, all claims databases have certain inherent limitations because the claims are collected for the purpose of payment, not research. Presence of a claim for a filled prescription does not indicate that the medication was consumed or that it was taken as prescribed. Similarly, absence of a claim for a filled prescription does not preclude the possibility of exposure to a medication. In addition, the use of medications such as acute migraine treatments taken as needed are challenging to capture with prescription data alone.

Medications filled over-the-counter, provided as samples by the physician, or received during an inpatient hospital stay will often not be observed in the claims data. Presence of a diagnosis code is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criterion rather than actual disease. Medical records will be reviewed for the primary study outcome MCM to confirm cases that are initially identified via claims.

The proposed algorithm to identify pregnant individuals with migraine requires claims-based evidence of migraine, including 2 or more diagnosis codes, 2 or more treatments, or 1 diagnosis code plus 1 treatment. The study groups are further restricted to individuals exposed to an acute migraine treatment during pregnancy. These inclusion criteria may tend to select individuals with moderate-to-severe migraine. While using a treated comparator group increases the study's internal validity (ie, exchangeability of the study cohorts), it reduces the external validity. Although these results will be generalizable to the population of individuals using acute migraine treatments during pregnancy, they may be less generalizable to individuals with milder disease.

The primary analysis is limited to confirmed MCMs among the subset of pregnancies resulting in a livebirth that link to the infant's data. This analysis may miss MCMs that result in a spontaneous abortion, a stillbirth, or MCMs among non-linked infants. Sensitivity analyses will be conducted to quantify and describe the impact this may have on the observed relative risks.

MCMs will be identified in liveborn infants, and study drug exposure will be assessed in the first trimester (Table 4). However, the exact timing of the development of malformations is

typically unknown. While major malformations typically originate in the first trimester, whether the malformation began to develop before drug exposure will be unknown for some pregnancies. For example, if the malformation began to develop at gestational week 8 and study drug exposure began at gestational week 10.

Although ICD-10-CM Z3A codes denoting gestational age may identify some spontaneous abortions that did not receive an ICD-10-CM spontaneous abortion diagnosis code, others may go unrecognized if the mother did not seek medical care. Additionally, while the use of ICD-10-CM Z3A codes to estimate LMP is valid (Chomistek et al. 2023), not all pregnancies have Z3A codes, and some degree of measurement error is expected in estimating the beginning of pregnancy. The resulting exposure misclassification due to estimated LMP, and consequently, the EDC, is not expected to be differential with respect to exposure. A sensitivity analysis may explore alternative exposure windows that are more and less conservative.

Residual confounding is always a concern in observational studies. While propensity score models can account for a large number of measured pre-specified and empirically derived variables, some variables may have a greater degree of misclassification, and some confounders may not be measured. For example, due to code limitations, claims data tend to have incomplete capture of smoking status. However, the degree of residual confounding due to unmeasured factors may be reduced if proxies of unmeasured factors are included in the models (Guertin et al. 2016). A quantitative bias analysis will assess the impact of residual confounding on the observed results.

The nonmigraine cohort will provide useful context in terms of background outcome prevalence estimates in commercially insured individuals where data is collected for healthcare administrative purposes. However, it cannot be directly compared to the migraine cohorts because of potential confounding. Hence, comparative analyses will be limited to the migraine cohorts, which will be balanced on potential confounders via propensity score matching.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient information

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

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws. There is no planned transfer of study data under this study protocol.

10.2. Patient consent

As this study does not involve data subject to privacy laws according to applicable legal requirements, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents from the relevant IRBs/IECs (eg, Biomedical Research Alliance of New York IRB, also known as BRANY). All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

10.4. 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 GPP issued by ISPE, and the European Medicines Agency, ENCePP Guide on Methodological Standards in Pharmacoepidemiology.

The conduct and reporting of this study follows Optum Epidemiology's SOPs that are consistent with the ISPE's GPP (ISPE 2015).

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not involve medical record review by the treating physician. External physician adjudicators will review medical records to confirm select outcomes among a subset of patients, as described in Section 9.3.2.2.

11.1. Structured data analysis

This study involves data that exist as structured data by the time of study start. In these data sources it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11.2. Human review of unstructured data

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, x-rays, or narrative fields in a database. The reviewer (study team) is obligated to report AEs with explicit attribution to any Pfizer drug that appear in the reviewed information (defined

per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

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

- All serious and non-serious AEs with explicit attribution to **any Pfizer drug** that appear in the reviewed information must be recorded on the data collection tool and reported, within 1 business day of awareness of the study team awareness and of the study team's determination that all criteria are met for reporting, to Pfizer Safety using the NIS AEM Report Form.
- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, 1 business day of awareness and of the study team's determination that all criteria are met for reporting, to Pfizer Safety using the NIS AEM Report Form.
- For exposure during pregnancy in studies of pregnant individuals, data on the exposure to zavegepant during pregnancy, are not reportable unless associated with serious or non-serious adverse events.
- For these AEs with an explicit attribution or scenarios involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is captured in the Event Narrative section of the report form, and constitutes all clinical information known regarding these AEs. No follow-up on related AEs will be conducted.

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

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

All Optum research staff members involved in the review of medical charts and completion of the NIS AEM Report Form must complete the following Pfizer training requirements:

- "Your Reporting Responsibilities (YRR) With Supplemental Topics."

These trainings must be completed by Optum research staff members prior to the start of unstructured data collection. All trainings include a "Confirmation of Training Certificate"

(for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The final study report will be posted on the EU PAS register. Manuscripts based on specific outcomes of interest may be developed for publication purposes.

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 Optum becomes aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

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None.

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. MEDICATIONS FOR THE TREATMENT OF MIGRAINE

Table 9. Medications for the treatment of migraine

Category	Drug(s)		Codes	Comments
CGRP receptor antagonist (acute & preventive)	Zavegepant (acute) Rimegepant (acute & preventive) Ubrogepant (acute) Atogepant (preventive)		NDCs HICL	Not currently recommended during pregnancy due to lack of evidence.
Prescription NSAIDs (acute)	Celecoxib Diclofenac Diflunisal Etodolac Fenoprofen Flurbiprofen Ibuprofen Indomethacin Ketoprofen Ketorolac	Mefenamic acid Meloxicam Nabumetone Naproxen Oxaprozin Piroxicam Sulindac Tolmetin Valdecoxib	HICL	Includes parenteral forms and solid oral forms (tablets, pills; not liquid forms that are expected to be pediatric preparations) NSAIDs will be designated as migraine medication if the individual does not have diagnosis codes for pain conditions (musculoskeletal pain, osteoarthritis, rheumatoid arthritis, other pain conditions) as defined in Section 9.3.3 ascertained using all available data before and including date of conception and through the end of pregnancy. Source of medication list: FDA (2018), Wood et al. (2021) Over-the-counter medications are not included. For use during second trimester of pregnancy only
ASA (acute)	Acetyl-salicylic acid (ASA), also known as aspirin		HICL	Does not include low-dose ASA, used for cardiovascular prevention. Over-the-counter medications are not included.
Acetaminophen (acute)	Acetaminophen*		HICL	Over-the-counter medications are not included. ACOG recommended as initial therapy for treatment of acute migraine during pregnancy.
Triptans (acute)	Almotriptan Eletriptan Frovatriptan Naratriptan	Rizatriptan Sumatriptan Zolmitriptan	HICL	Recommended for second-line treatment of migraine during pregnancy; sumatriptan has the most extensive safety profile.
Ditans (acute)	Lasmiditan		HICL	Not currently recommended during pregnancy due to lack of evidence.

Table 9. Medications for the treatment of migraine

Category	Drug(s)		Codes	Comments
Ergots (acute)	Dihydroergotamine	Ergotamine	HICL	Safety concern during pregnancy because of an increased risk of spontaneous abortion.
Opioids (acute)	Buprenorphine Butorphanol Codeine Ethoheptazine Fentanyl Hydrocodone Dihydrocodeine Dihydrocodeinone Dezocine Hydromorphone Levorphanol Meperidine	Methadone Morphine Nalbuphine Opium Tincture Oxycodone Oxymorphone Pentazocine Propoxyphene Sufentanil Tapentadol Tramadol	HICL	Includes all parenteral and oral forms. Sources: NIDA (2020), Wood et al. (2021) Over-the-counter medications are not included. Not recommended for treatment of migraine during pregnancy.
Beta-blockers (preventive)	Atenolol Bisoprolol Carvedilol Esmolol Labetalol Metoprolol	Nadolol Pindolol Propranolol Sotalol Timolol	HICL	Does not include ophthalmic forms. Beta-blockers will be designated as migraine medication if the individual does not have diagnosis codes for hypertension as defined in Section 9.3.3, ascertained using all available data before and including EDC and through the end of pregnancy, or if the individual has gestational hypertension, using all available data before and including EDC and through the end of pregnancy.
Anti-epileptics (preventive)	Clonazepam Carbamazepine Diazepam Divalproex Gabapentin Levetiracetam	Lorazepam Sodium valproate Topiramate Valproate Valproic acid Valproate semisodium	HICL	Anti-epileptics will be designated as migraine medication if the individual does not have diagnosis codes for epilepsy as defined in Section 9.3.3, ascertained using all available data before and including EDC and through the end of pregnancy. Topiramate and valproic acid are not recommended in pregnancy.

Table 9. Medications for the treatment of migraine

Category	Drug(s)		Codes	Comments
Antidepressants (preventive)	Amitriptyline Bupropion Citalopram Duloxetine Fluoxetine Nefazodone	Nortriptyline Paroxetine Sertraline Trazodone Venlafaxine	HICL	Antidepressants will be designated as migraine medication if the individual does not have diagnosis codes for depression, bipolar disorders, anxiety or panic disorders, or obsessive-compulsive disorder as defined in Section 9.3.3, ascertained using all available data before and including date of conception and through the end of pregnancy.
Botulinum toxin (preventive)	OnabotulinumtoxinA		HICL	CPT®[5] code 64615 is specific for chronic migraine. Use for some FDA-approved indications is not of interest for this study: overactive bladder, urinary incontinence, detrusor overactivity, spasticity, cervical dystonia, axillary hyperhidrosis, blepharospasm or strabismus (BOTOX Prescribing Information 2021).
CGRP monoclonal antibodies (preventive)	Eptinezumab Erenumab	Fremanezumab Galcanezumab	HICL	Not recommended during pregnancy at this time, stop 6 months before pregnancy
Antinauseants (acute)	Meclizine Metoclopramide* Ondansetron Granisetron	Palonosetron Rolapitant Tolazamide	HICL	Indicated for nausea.
Antipsychotics (acute)	Risperidone Paliperidone Aripiprazole	Quetiapine Haloperidol Olanzapine	HICL	Not indicated for migraine.
Steroid (preventive)	Corticosteroids		HICL	Used with abortive therapy to reduce headache recurrence.
Antihistamines (acute)	Chlorpheniramine Cyproheptadine Diphenhydramine* Phenyltoloxamine		HICL	Diphenhydramine is recommended with metoclopramide as a first-line treatment during pregnancy. Others not indicated for migraine.
Barbiturates	Butalbital Phenobarbital		HICL	Butalbital is not recommended for the treatment of migraine during pregnancy.

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Table 9. Medications for the treatment of migraine

Category	Drug(s)	Codes	Comments
Other	Aspirin Meprobamate (anxiolytic) Dipyridamole (antiplatelet) Pseudoephedrine Phenacetin (analgesics) Salicylamide (analgesics) Carisoprodol (muscle relaxant) Methocabamol Orphenadrine (muscle relaxant)	HICL	Aspirin should be avoided for migraine.

Abbreviations: ACOG, American College of Obstetricians and Gynecologists; ASA, acetyl-salicylic acid; CGRP, calcitonin gene–related peptide; FDA, Food and Drug Administration; HICL, hierarchical ingredient code list; NSAID, nonsteroidal anti-inflammatory drug.
* Drug is indicated during pregnancy per ACOG Clinical Practice Guidelines.
Note: HICL codes are proprietary to First Databank. The list of medications will be updated as new medications are approved over the course of the study. Updates will be made before each annual interim analysis.

ANNEX 3. LIST OF TERATOGENIC MEDICATIONS

Table 10. List of known teratogenic medications

Drug class/generic name	Half-life	Relevant exposure window
Androgens		
Methyltestosterone	6 to 8 h	First, second, and third trimesters
Testosterone	Plasma half-life of testosterone ranges from 10 to 100 min. The cypionate and enanthate esters of testosterone have longer durations of action than testosterone. Cypionate half-life is about 8 d.	First, second, and third trimesters
Mesterolone	12 to 13 h	Not in TERIS. Assumed window: first, second, and third trimesters
Nandrolone	144 to 288 h	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

Table 10. List of known teratogenic medications

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-	Unknown. Assumed window: first, second, and third trimesters

Table 10. List of known teratogenic medications

Drug class/generic name	Half-life	Relevant exposure window
	release tablet, 7 to 11 h 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.

Table 10. List of known teratogenic medications

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

Table 10. List of known teratogenic medications

Drug class/generic name	Half-life	Relevant exposure window
Erlotinib	36.2 h	2 weeks before conception and first, second, and third trimesters
Estramustine	10 to 20 h	Not in TERIS. Assumed window: first, second, and third trimesters
Etoposide	4 to 11 h	6 months before conception and first, second, and third trimesters
Fludarabine	20 h	6 months before conception and first, second, and third trimesters
Fluorouracil	8 to 20 min	3 months before conception and first, second, and third trimesters
Gemcitabine	1.7 to 19.4 h	6 months before conception and first, second, and third trimesters
Hydroxycarbamide	2 to 4.5 h	Unknown. Assumed window: first, second, and third trimesters
Idarubicin	20 to 22 h	6.5 months before conception and first, second, and third trimesters
Ifosfamide	15 h	Unknown. Assumed window: first, second, and third trimesters
Imatinib	18 h	2 weeks before conception and first, second, and third trimesters
Irinotecan	6 to 12 h	6 months before conception and first, second, and third trimesters
Lapatinib	24 h	1 week before conception and first, second, and third trimesters
Lomustine	16 to 48 h	2 weeks before conception and first, second, and third trimesters
Melphalan	10 to 75 min	Unknown. Assumed window: first, second, and third trimesters
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

Table 10. List of known teratogenic medications

Drug class/generic name	Half-life	Relevant exposure window
Pentostatin	5.7 h	Not in TERIS. Assumed window: first, second, and third trimesters
Procarbazine	IV, approximately 10 min	Not in TERIS. Assumed window: first, second, and third trimesters
Raltitrexed	260 h	6 months before conception and first, second, and third trimesters
Sorafenib	25 to 48 h	6 months before conception and first, second, and third trimesters
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

Table 10. List of known teratogenic medications

Drug class/generic name	Half-life	Relevant exposure window
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		
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

Table 10. List of known teratogenic medications

Drug class/generic name	Half-life	Relevant exposure window
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
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

Table 10. List of known teratogenic medications

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

ANNEX 4. OUTCOME CODE LISTS

Table 11. Pregnancy and infant outcome code lists

Outcome	Type	Code(s)	Code Description
Spontaneous abortion	ICD-10-CM	O02.1	Missed abortion
Spontaneous abortion	ICD-10-CM	O03**	Spontaneous abortion
Spontaneous abortion	CPT®[6]	59800	Treatment Of Spontaneous Abortion, First Trimester
Spontaneous abortion	CPT	59801	Treatment Of Spontaneous Abortion, First Trimester
Spontaneous abortion	CPT	59810	Treatment Of Spontaneous Abortion, Second Trimester
Spontaneous abortion	CPT	59811	Treatment Of Spontaneous Abortion, Second Trimester
Stillbirth	ICD-10-CM	Z37.1	Single stillbirth
Stillbirth	ICD-10-CM	Z37.3	Twins, one liveborn and one stillborn
Stillbirth	ICD-10-CM	Z37.6*	Other multiple births, some liveborn
Stillbirth	ICD-10-CM	Z37.4	Twins, both stillborn
Stillbirth	ICD-10-CM	Z37.7	Other multiple births, all stillborn
Stillbirth	ICD-10-CM	O31.00	Papyraceous fetus, unspecified trimester
Stillbirth	ICD-10-CM	O31.02	Papyraceous fetus, second trimester
Stillbirth	ICD-10-CM	O3103X0	Papyraceous fetus, third trimester, not applicable or unsp
Stillbirth	ICD-10-CM	P95	Stillbirth
Stillbirth	ICD-10-CM	O36.4	Maternal care for intrauterine death
Pre-eclampsia	ICD-10-CM	O14*	Pre-eclampsia
Eclampsia	ICD-10-CM	O15**	Eclampsia
Gestational diabetes	ICD-10-CM	O24.4**	Gestational diabetes mellitus
Gestational diabetes	CPT	82951	Glucose tolerance test
Gestational diabetes	CPT	82952	Glucose tolerance test – added samples
Gestational hypertension	ICD-10-CM	O13***	Gestational [pregnancy-induced] hypertension without significant proteinuria
Preterm birth	ICD-10-CM	O60.10X0 – O60.14X9	Preterm labor with preterm delivery
Preterm birth	ICD-10-CM	Z3A.22-Z3A.66	22-36 weeks of gestation
Preterm birth	ICD-10-CM	P07.0*	Extremely low birth weight newborn
Preterm birth	ICD-10-CM	P07.1*	Other low birth weight newborn
Preterm birth	ICD-10-CM	P07.20 – P07.26	Extreme immaturity of newborn

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Table 11. Pregnancy and infant outcome code lists

Outcome	Type	Code(s)	Code Description
Preterm birth	ICD-10-CM	P07.30-P07.39	Preterm [premature] newborn [other]
Preterm birth	ICD-10-CM	P10.2	Intraventricular hemorrhage due to birth injury
Preterm birth	ICD-10-CM	P22.0	Respiratory distress syndrome of newborn
Preterm birth	ICD-10-CM	P27*	Chronic respiratory disease originating in the perinatal period
Preterm birth	ICD-10-CM	P52.0	Intraventricular (nontraumatic) hemorrhage, grade 1, of newborn
Preterm birth	ICD-10-CM	P52.1	Intraventricular (nontraumatic) hemorrhage, grade 2, of newborn
Preterm birth	ICD-10-CM	P52.2*	Intraventricular (nontraumatic) hemorrhage, grade 3 and grade 4, of newborn
Preterm birth	ICD-10-CM	P52.3	Unspecified intraventricular (nontraumatic) hemorrhage of newborn
Preterm birth	ICD-10-CM	P59.0	Neonatal jaundice associated with preterm delivery
Preterm birth	ICD-10-CM	P61.2	Anemia of prematurity
Preterm birth	ICD-10-CM	P77*	Necrotizing enterocolitis of newborn
Preterm birth	ICD-10-CM	Q25.0	Patent ductus arteriosus
Small for gestational age	ICD-10-CM	P05.1*	Newborn small for gestational age
Small for gestational age	ICD-10-CM	O36.511*	Maternal care for known or suspected placental insufficiency, first trimester
Small for gestational age	ICD-10-CM	O36.512*	Maternal care for known or suspected placental insufficiency, second trimester
Small for gestational age	ICD-10-CM	O36.513*	Maternal care for known or suspected placental insufficiency, third trimester
Small for gestational age	ICD-10-CM	O36.519*	Maternal care for known or suspected placental insufficiency, unspecified trimester
Small for gestational age	ICD-10-CM	O36.591	Maternal care for other known or suspected poor fetal growth, first trimester
MCM	ICD-10-CM	Q00*	Anencephaly and similar malformations
MCM	ICD-10-CM	Q01*	Encephalocele
MCM	ICD-10-CM	Q02	Microcephaly
MCM	ICD-10-CM	Q03*	Congenital hydrocephalus
MCM	ICD-10-CM	Q04*	Other congenital malformations of brain
MCM	ICD-10-CM	Q05*	Spina bifida
MCM	ICD-10-CM	Q06*	Other congenital malformations of spinal cord
MCM	ICD-10-CM	Q07**	Other congenital malformations of nervous system
MCM	ICD-10-CM	Q10*	Congenital malformations of eyelid, lacrimal apparatus and orbit

Table 11. Pregnancy and infant outcome code lists

Outcome	Type	Code(s)	Code Description
MCM	ICD-10-CM	Q11*	Anophthalmos, microphthalmos and microphthalmos
MCM	ICD-10-CM	Q12*	Congenital lens malformations
MCM	ICD-10-CM	Q13**	Congenital malformations of anterior segment of eye
MCM	ICD-10-CM	Q14*	Congenital malformations of posterior segment of eye
MCM	ICD-10-CM	Q15*	Other congenital malformations of eye
MCM	ICD-10-CM	Q16*	Congenital malformations of ear causing impairment of hearing
MCM	ICD-10-CM	Q17*	Other congenital malformations of ear
MCM	ICD-10-CM	Q18*	Other congenital malformations of face and neck
MCM	ICD-10-CM	Q20*	Congenital malformations of cardiac chambers and connections
MCM	ICD-10-CM	Q21**	Congenital malformations of cardiac septa
MCM	ICD-10-CM	Q22*	Congenital malformations of pulmonary and tricuspid valves
MCM	ICD-10-CM	Q23*	Congenital malformations of aortic and mitral valves
MCM	ICD-10-CM	Q24*	Other congenital malformations of heart
MCM	ICD-10-CM	Q25**	Congenital malformations of great arteries
MCM	ICD-10-CM	Q26*	Congenital malformations of great veins
MCM	ICD-10-CM	Q27**	Other congenital malformations of peripheral vascular system
MCM	ICD-10-CM	Q28*	Other congenital malformations of circulatory system
MCM	ICD-10-CM	Q30*	Congenital malformations of nose
MCM	ICD-10-CM	Q31*	Congenital malformations of larynx
MCM	ICD-10-CM	Q32*	Congenital malformations of trachea and bronchus
MCM	ICD-10-CM	Q33*	Congenital malformations of lung
MCM	ICD-10-CM	Q34*	Other congenital malformations of respiratory system
MCM	ICD-10-CM	Q35*	Cleft palate
MCM	ICD-10-CM	Q36*	Cleft lip
MCM	ICD-10-CM	Q37*	Cleft palate with cleft lip
MCM	ICD-10-CM	Q38*	Other congenital malformations of tongue, mouth and pharynx
MCM	ICD-10-CM	Q39*	Congenital malformations of esophagus
MCM	ICD-10-CM	Q40*	Other congenital malformations of upper alimentary tract

Table 11. Pregnancy and infant outcome code lists

Outcome	Type	Code(s)	Code Description
MCM	ICD-10-CM	Q41*	Congenital absence, atresia and stenosis of small intestine
MCM	ICD-10-CM	Q42*	Congenital absence, atresia and stenosis of large intestine
MCM	ICD-10-CM	Q43*	Other congenital malformations of intestine
MCM	ICD-10-CM	Q44*	Congenital malformations of gallbladder, bile ducts and liver
MCM	ICD-10-CM	Q45*	Other congenital malformations of digestive system
MCM	ICD-10-CM	Q50**	Congenital malformations of ovaries, fallopian tubes and broad ligaments
MCM	ICD-10-CM	Q51***	Congenital malformations of uterus and cervix
MCM	ICD-10-CM	Q52***	Other congenital malformations of female genitalia
MCM	ICD-10-CM	Q53***	Undescended and ectopic testicle
MCM	ICD-10-CM	Q54*	Hypospadias
MCM	ICD-10-CM	Q55**	Other congenital malformations of male genital organs
MCM	ICD-10-CM	Q56*	Indeterminate sex and pseudohermaphroditism
MCM	ICD-10-CM	Q60*	Renal agenesis and other reduction defects of kidney
MCM	ICD-10-CM	Q61**	Cystic kidney disease
MCM	ICD-10-CM	Q62**	Congenital obstructive defects of renal pelvis and congenital malformations of ureter
MCM	ICD-10-CM	Q63*	Other congenital malformations of kidney
MCM	ICD-10-CM	Q64**	Other congenital malformations of urinary system
MCM	ICD-10-CM	Q65**	Congenital deformities of hip
MCM	ICD-10-CM	Q66***	Congenital deformities of feet
MCM	ICD-10-CM	Q67*	Congenital musculoskeletal deformities of head, face, spine and chest
MCM	ICD-10-CM	Q68*	Other congenital musculoskeletal deformities
MCM	ICD-10-CM	Q69*	Polydactyly
MCM	ICD-10-CM	Q70**	Syndactyly
MCM	ICD-10-CM	Q71***	Reduction defects of upper limb
MCM	ICD-10-CM	Q72***	Reduction defects of lower limb
MCM	ICD-10-CM	Q73*	Reduction defects of unspecified limb
MCM	ICD-10-CM	Q74*	Other congenital malformations of limb(s)
MCM	ICD-10-CM	Q75*	Other congenital malformations of skull and face bones

Table 11. Pregnancy and infant outcome code lists

Outcome	Type	Code(s)	Code Description
MCM	ICD-10-CM	Q76***	Congenital malformations of spine and bony thorax
MCM	ICD-10-CM	Q77*	Osteochondrodysplasia with defects of growth of tubular bones and spine
MCM	ICD-10-CM	Q78*	Other osteochondrodysplasias
MCM	ICD-10-CM	Q79**	Congenital malformations of musculoskeletal system, not elsewhere classified
MCM	ICD-10-CM	Q80*	Congenital ichthyosis
MCM	ICD-10-CM	Q81*	Epidermolysis bullosa
MCM	ICD-10-CM	Q82*	Other congenital malformations of skin
MCM	ICD-10-CM	Q83*	Congenital malformations of breast
MCM	ICD-10-CM	Q84*	Other congenital malformations of integument
MCM	ICD-10-CM	Q85**	Phakomatoses, not elsewhere classified
MCM	ICD-10-CM	Q86*	Congenital malformation syndromes due to known exogenous causes, not elsewhere classified
MCM	ICD-10-CM	Q87***	Other specified congenital malformation syndromes affecting multiple systems
MCM	ICD-10-CM	Q89**	Other congenital malformations, not elsewhere classified

Abbreviations: CPT[7], Current Procedural Terminology codes; ICD-10-CM, International Classification of Diseases,10th Revision, Clinical Modification; MCM, major congenital malformation; TERIS, teratogen information system.
* Indicates how many additional decimal places should be included in the wildcard for billable codes only.

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ANNEX 5. OPERATIONAL DEFINTIONS OF COVARIATES

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
Demographic and general characteristics						
Age	On date of conception	[Date of date of conception– mother's date of birth]/365.25	Continuous variable in years Categorical variable: 15-34 years, ≥ 35 years			
Race and ethnicity	On date of conception	Self-reported	• Asian • Black • Hispanic • White • Other and unknown			
Duration of health plan enrollment	On date of conception	[Date of date of conception – mother's date of health plan enrollment]/365.25	Continuous variable in years Categorical variable: < 1 year, 1-2 years, 3-4 years, ≥ 5 years			
Year of pregnancy start	On date of conception	Calendar year of date of conception for current pregnancy	Year			
Year of pregnancy end	On pregnancy end date	Calendar year of end of current pregnancy	Year			
Geographic region	On date of conception	US region of residence	• Northeast • West			

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
			• Midwest • South • Unknown			
Prior history of medical conditions						
Depression and bipolar disorders	All available data within 6 months before and including date of conception	Defined through diagnosis codes and applicable medications	Present/absent	ICD-10	F30*	Manic episode
					F31*	Bipolar disorder
					F32*	Major Depressive disorder, single episode
					F33*	Major depressive disorder, recurrent
					F34.1	Dysthymic disorder
				AHFS	281604**	Antidepressants
Anxiety and panic disorders	All available data within 6 months before and including date of conception	Defined through diagnosis codes and applicable medications	Present/absent	ICD-10	F40* F41*	Phobic anxiety disorders Other anxiety disorders
				AHFS	282492**	Anxiolytics, sedatives, and hypnotics
Obsessive-compulsive disorder	All available data within 6 months before and including date of conception	Defined through diagnosis codes and applicable medications	Present/absent	ICD-10	F42*	Obsessive compulsive disorder
Schizophrenia	All available data within 6 months before and including date of conception	Defined through diagnosis codes and applicable medications	Present/absent	ICD-10 HICL	F20*	Schizophrenia
Epilepsy[a]	All available data within 6 months before and including date of conception	Defined through diagnosis codes and applicable medications	Present/absent	ICD-10 HICL	G40*	Epilepsy Carbamazepine, clonazepam, divalproex, gabapentin, levetiracetam, lorazepam, topiramate, valproate, valproic acid

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
Seizures[b]	All available data within 6 months before and including date of conception and during pregnancy	Defined through diagnosis codes and applicable medications	Present/absent	ICD-10 HICL	R56*	Convulsions, not elsewhere classified
Alcohol misuse	All available data within 6 months before and including date of conception and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy	ICD-10	F10*	Alcohol related disorders
					E52	Niacin deficiency
					G62.1 I42.6	Alcoholic polyneuropathy Alcoholic cardiomyopathy
					K29.2	Alcoholic gastritis
					K70.0	Alcoholic fatty liver
					K70.3*	Alcoholic cirrhosis of liver
					K70.9	Alcoholic liver disease, unspecified
					T51*	Toxic effect of alcohol
					Z71.4*	Alcohol abuse counseling and surveillance
Drug misuse	All available data within 6 months before and including date of conception and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy	ICD-10	F11*	Opioid related disorders
					F12*	Cannabis related disorders
					F13*	Sedative, hypnotic, or anxiolytic related disorders
					F14*	Cocaine related disorders
					F15*	Other stimulant related disorders
					F16*	Hallucinogen related disorders
					F18*	Inhalant related disorders

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					F19*	Other psychoactive substance related disorders
Hyperlipidemia	All available data within 6 months before and including date of conception	Defined through diagnosis codes and applicable medications	Present/absent	ICD-10	E78.0*	Pure hypercholesterolemia
					E78.1	Pure hyperglyceridemia
					E78.2	Mixed hyperlipidemia
					E78.3	Hyperchylomicronemia
					E78.4*	Other hyperlipidemia
					E78.5	Hyperlipidemia, unspecified
Diabetes	All available data within 6 months before and including date of conception	Defined through diagnosis codes not including gestational diabetes	Present/absent	ICD-10	E10*	Type 1 diabetes mellitus
					E11*	Type 2 diabetes mellitus
					E13*	Other specified diabetes mellitus
Hypertension	All available data within 6 months before and including date of conception	Defined through diagnosis codes, not including gestational hypertension	Present/absent	ICD-10	I10	Essential (primary) hypertension
					I11*	Hypertensive heart disease
					I12*	Hypertensive chronic kidney disease
					I13*	Hypertensive heart and chronic kidney disease
					I15*	Secondary hypertension
					I67.4	Hypertensive encephalopathy
					N26.2	Page kidney
Malignancy	All available data before and including date of conception	Defined through diagnosis codes	Present/absent	ICD-10	C00-C96	Malignancies
					D45*	Polycythemia vera
					D46*	Myelodysplastic syndromes
Thyroid disease	All available data within 6 months before and including date of conception	Defined through diagnosis codes	Present/absent	ICD-10	E00*	Congenital iodine-deficiency syndrome
					E01*	Iodine-deficiency related thyroid disorders and allied conditions
					E02*	Subclinical iodine-deficiency hypothyroidism

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					E03*	Other hypothyroidism
					E04*	Other nontoxic goiter
					E05*	Thyrotoxicosis [hyperthyroidism]
					E06*	Thyroiditis
					E07*	Other disorders of thyroids
					E89.0	Postprocedural hypothyroidism
Respiratory disease including asthma	All available data within 6 months before and including date of conception	Defined through diagnosis codes	Present/absent	ICD-10	I26.0*	Pulmonary embolism
					I27.2*	Other secondary pulmonary hypertension
					I27.8*	Other specified pulmonary diseases
					I27.9*	Pulmonary heart disease, unspecified
					J40*	Bronchitis, not specified as acute or chronic
					J41*	Simple and mucopurulent chronic bronchitis
					J42*	Unspecified chronic bronchitis
					J43*	Emphysema
					J44*	Other chronic obstructive pulmonary disease
					J45*	Asthma
					J47*	Bronchiectasis
					J60*	Coal worker’s pneumoconiosis
					J61*	Pneumoconiosis due to asbestos and other mineral fibers
					J62*	Pneumoconiosis due to dust containing silica
					J63*	Pneumoconiosis due to other inorganic dusts
					J64*	Unspecified pneumoconiosis

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					J65*	Pneumoconiosis associated with tuberculosis
					J66*	Airway disease due to specific organic dust
					J67*	Hypersensitivity pneumonitis due to organic dust
					J68.4*	Chronic respiratory conditions due to chemicals, gases, fumes, and vapors
					J70.1*	Chronic and other pulmonary manifestations due to radiation
					J70.3*	Chronic drug-induced interstitial lung disorders
Liver disease	All available data within 6 months before and including date of conception	Defined through diagnosis codes	Present/absent	ICD-10	B18*	Chronic viral hepatitis
					I85*	Esophageal varices
					I86.4	Gastric varices
					K70*	Alcoholic liver disease
					K71.1*	Toxic liver disease with hepatic necrosis
					K71.3	Toxic liver disease with chronic persistent hepatitis
					K71.4	Toxic liver disease with chronic lobular hepatitis
					K71.5*	Toxic liver disease with chronic active hepatitis
					K71.7	Toxic liver disease with fibrosis and cirrhosis of liver
					K72.1*	Chronic hepatic failure
					K72.9*	Hepatic failure, unspecified
					K73*	Chronic hepatitis, not elsewhere classified
					K74*	Fibrosis and cirrhosis of liver
					K75.4	Autoimmune hepatitis

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					K75.81	Nonalcoholic steatohepatitis (NASH)
					K76.0	Fatty (change of) liver, not elsewhere classified
					K76.2	Central hemorrhagic necrosis of liver
					K76.3	Infarction of liver
					K76.5	Hepatic veno-occlusive disease
					K76.6	Portal hypertension
					K76.7	Hepatorenal syndrome
					K76.81	Hepatopulmonary syndrome
					K76.89	Other specified diseases of liver
					K76.9	Liver disease, unspecified
					Z48.23	Encounter for aftercare following liver transplant
					Z94.4	Liver transplant status
Chronic kidney disease	All available data within 6 months before and including date of conception	Defined through diagnosis codes and procedures	Present/absent	ICD-10	I12.0	Hypertensive chronic kidney disease with stage 5 chronic kidney disease or end stage renal disease
					I13.1	Hypertensive heart and chronic kidney disease without heart failure
					N03.2	Chronic nephritic syndrome with diffuse membranous glomerulonephritis
					N03.3	Chronic nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
					N03.4	Chronic nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					N03.5	Chronic nephritic syndrome with diffuse mesangiocapillary glomerulonephritis
					N03.6	Chronic nephritic syndrome with dense deposit disease
					N03.7	Chronic nephritic syndrome with diffuse crescentic glomerulonephritis
					N05.2	Unspecified nephritic syndrome with diffuse membranous glomerulonephritis
					N05.3	Unspecified nephritic syndrome with diffuse mesangial proliferative glomerulonephritis
					N05.4	Unspecified nephritic syndrome with diffuse endocapillary proliferative glomerulonephritis
					N05.5	Unspecified nephritic syndrome with diffuse mesangiocapillary glomerulonephritis
					N05.6	Unspecified nephritic syndrome with dense deposit disease
					N05.7	Unspecified nephritic syndrome with diffuse crescentic glomerulonephritis
					N18*	Chronic kidney disease (CKD)
					N25.0	Renal osteodystrophy
					Z49.0*	Preparatory care for renal dialysis
					Z49.31	Encounter for adequacy testing for hemodialysis
					Z91.15	Patient’s noncompliance with renal dialysis

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					Z94.0	Kidney transplant status
					Z99.2	Dependence on renal dialysis
Obesity	All available data within 6 months before and including date of conception	Defined through diagnosis codes and proxies (applicable medications and procedures)	Present/absent	ICD-10	E66*	Overweight and obesity
					O99.21*	Obesity complicating pregnancy, childbirth, and the puerperium
				HCPCS	Z68.3*	Body mass index (BMI), 30-39, adult
					Z68.4*	Body mass index (BMI), 40 +, adult
					G0447	Face-to-face behavioral counseling for obesity, 15 minutes
					G0473	Face-to-face behavioral counseling for obesity, group (2-10), 30 minutes
Smoking	Available data within 6 months before and including date of conception and during pregnancy	Defined through diagnosis codes and proxies (applicable medications)	Present/absent Pre-pregnancy, by trimester of pregnancy	ICD-10	F17*	Nicotine dependence
					O99.33*	Tobacco use disorder complicated pregnancy, childbirth, and the puerperium
					T65.22* Z53.01	Toxic effects of tobacco cigarettes Procedure and treatment not carried out due to patient smoking
					Z71.6	Tobacco abuse counseling
					Z72.0	Tobacco use
					Z87.891	Personal history of nicotine dependence

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
				CPT®[8]	99406	Smoking and tobacco use cessation counseling visit; intermediate, greater than 3 minutes up to 10 minutes
					99407	Smoking and tobacco use cessation counseling visit; intensive, greater than 10 minutes
Cardiovascular diseases	All available data within 6 months before and including date of conception	Defined through diagnosis codes	Present/absent	ICD-10	A18.84	Tuberculosis of heart
					A52.0	Cardiovascular and cerebrovascular syphilis
					E08.51	Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy without gangrene
					E08.52	Diabetes mellitus due to underlying condition with diabetic peripheral angiopathy with gangrene
					E09.51	Drug or chemical induced diabetes mellitus with diabetic peripheral angiopathy without gangrene
					E09.52	Drug or chemical induced diabetes mellitus with diabetic peripheral angiopathy with gangrene

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Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					E10.51	Type 1 diabetes mellitus with diabetic peripheral angiopathy without gangrene
					E10.52	Type 1 diabetes mellitus with diabetic peripheral angiopathy with gangrene
					E11.51	Type 2 diabetes mellitus with diabetic peripheral angiopathy without gangrene
					E13.51	Other specified diabetes mellitus with diabetic peripheral angiopathy without gangrene
					E13.52	Other specified diabetes mellitus with diabetic peripheral angiopathy with gangrene
					G45*	Transient cerebral ischemic attacks and related syndromes
					G46*	Vascular syndromes of brain in cerebrovascular diseases
					H34.0*	Transient retinal artery occlusion
					I00 – I99	Diseases of the circulatory system
					K55.1	Chronic vascular disorders of intestine
					K55.8	Other vascular disorders of intestine
					K55.9	Vascular disorder of intestine, unspecified
					Q23.0	Congenital stenosis of aortic valve
					Q23.1	Congenital insufficiency of aortic valve

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					Q23.2	Congenital mitral stenosis
					R00.0	Tachycardia, unspecified
					R00.1	Bradycardia, unspecified
					R00.8	Other abnormalities of heartbeat
					T82.1*	Mechanical complication of cardiac electronic device
					Z45.0*	Encounter for adjustment and management of cardiac device
					Z95.0*	Presence of cardiac pacemaker
					Z95.2	Presence of prosthetic heart valve
					Z95.3	Presence of other heart valve replacement
					Z95.4	Presence of other heart valve replacement
					Z95.810	Presence of automatic (implantable) cardiac defibrillator
					Z95.818	Presence of other cardiac implants and grafts
					Z95.82*	Presence of other vascular implants and grafts
					Z95.9	Presence of cardiac and vascular implant and graft, unspecified
Pain conditions[c]	All available data within 6 months before and including date of conception	Defined through diagnosis codes	Present/absent	ICD-10	G50.0	Trigeminal neuralgia
					G54*	Nerve root and plexus disorders
					M05*	Rheumatoid arthritis with rheumatoid factor
					M06*	Other rheumatoid arthritis
					M07*	Enteropathic arthropathies
					M08*	Juvenile arthritis

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					M1A*	Chronic gout
					M10*	Gout
					M11*	Other crystal arthropathies
					M12*	Other and unspecified arthropathy
					M13*	Other arthritis
					M14*	Arthropathies in other diseases classified elsewhere
					M15*	Polyosteoarthritis
					M16*	Osteoarthritis of hip
					M17*	Osteoarthritis of knee
					M18*	Osteoarthritis of first carpometacarpal joint
					M19*	Other and unspecified osteoarthritis
					M50.0*	Cervical disc disorder with myelopathy
					M50.1*	Cervical disc disorder with radiculopathy
					M54*	Dorsalgia
Cluster headache	All available data within 6 months before and including date of conception	Defined through diagnosis codes	Present/absent	ICD-10	G44.00*	Cluster headache syndrome
					G44.01*	Episodic cluster headache
					G44.02*	Chronic cluster headache
Migraine type	All available data before and including date of conception and during pregnancy	Defined through diagnosis codes and applicable medications	Present/absent If migraine present, type of migraine categories:	ICD-10	G43***	Migraine
					G43.11*	Migraine with aura, intractable

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
			With aura, intractable	ICD-10	G43.51*	Persistent migraine aura without cerebral infarction, intractable
					G43.61*	Persistent migraine aura with cerebral infarction, intractable
			With aura, not intractable	ICD-10	G43.10*	Migraine with aura, not intractable
					G43.50*	Persistent migraine aura without cerebral infarction, not intractable
					G43.60*	Persistent migraine aura with cerebral infarction, not intractable
			Without aura, intractable	ICD-10	G43.01*	Migraine without aura, intractable
					G43.41*	Hemiplegic migraine, intractable
					G43.71*	Chronic migraine without aura, intractable
			Without aura, not intractable	ICD-10	G43.00*	Migraine without aura, not intractable
					G43.40*	Hemiplegic migraine, not intractable
					G43.70*	Chronic migraine without aura, not intractable
			Other	ICD-10	G43.A*	Cyclical vomiting
					G43.B*	Ophthalmoplegic migraine
					G43.C*	Periodic headache syndromes in child or adult

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					G43.D*	Abdominal migraine
					G43.8*	Other migraine
					G43.9*	Migraine, unspecified
Prior obstetric history						
Gravidity	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Number of pregnancies (0, 1, 2 or more)			Based on DAPI algorithms
Parity	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Number of vaginal deliveries or C-sections (0, 1, 2 or more)			Based on DAPI algorithms
Spontaneous abortions	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Present/absent			See Table 10
Spontaneous abortions	All available data within 6 months before current pregnancy including date of conception	Number of pregnancies ending in spontaneous abortion defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Number of pregnancies (0, 1, 2 or more)			See Table 10

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
Pregnancy terminations	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis and procedure codes	Present/absent	ICD-10	O04.5	Genital tract and pelvic infection following (induced) termination of pregnancy
					O04.6	Delayed or excessive hemorrhage following (induced) termination of pregnancy
					O04.7	Embolism following (induced) termination of pregnancy
					O04.8*	(Induced) termination of pregnancy with other and unspecified complications
					O07**	Failed attempted termination of pregnancy
					Z33.2	Encounter for elective termination of pregnancy
				ICD-10 Procedure	10A0***	Products of conception
				HCPCS	S0190	Mifepristone Oral 200mg
					S0191	Misoprostol Oral 200 mcg
					S0199	Medically induced abortion by oral ingestion of medication including all associated services and supplies
					S2260	Induced abortion, 17-24 weeks
					S2262	Abortion for maternal indication, 25 weeks or greater
					S2265	Induced abortion, 25-28 weeks
					S2266	Induced abortion, 29-31 weeks
					S2267	Induced abortion, 32 weeks/greater

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
				CPT[9]	01964	Anesthesia for abortion procedures
					01965	Anesthesia for incomplete or missed abortion procedures
					01966	Anesthesia for induced abortion procedures
					59840	Induced abortion, by dilation and curettage
					59841	Induced abortion, by dilation and evacuation
					59850	Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines
					59851	Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
					59852	Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and

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Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
						secundines; with hysterotomy (failed intra-amniotic injection)
					59855[10]	Induced abortion, by 1 or more vaginal suppositories (eg, prostaglandin) with or without cervical dilation (eg, laminaria), including hospital admission and visits, delivery of fetus and secundines
					59856	Induced abortion, by 1 or more vaginal suppositories (eg, prostaglandin) with or without cervical dilation (eg, laminaria), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
					59857	59857 Induced abortion, by 1 or more vaginal suppositories (eg, prostaglandin) with or without cervical dilation (eg, laminaria), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed intra-amniotic injection)
Preterm births	All available data within 3 years before current pregnancy	Defined through diagnosis codes	Present/absent	ICD-10	Z3A.22-Z3A.66	22-36 weeks of gestation
					P07.0*	Extremely low birth weight newborn

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Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
	including date of conception				P07.1*	Other low birth weight newborn
					P07.20 - P07.26	Extreme immaturity of newborn
					P07.30 - P07.39	Preterm [premature] newborn [other]
					P10.2	Intraventricular hemorrhage due to birth injury
					P22.0	Respiratory distress syndrome of newborn
					P27*	Chronic respiratory disease originating in the perinatal period
					P52.0	Intraventricular (nontraumatic) hemorrhage, grade 1, of newborn
					P52.1	Intraventricular (nontraumatic) hemorrhage, grade 2, of newborn
					P52.2*	Intraventricular (nontraumatic) hemorrhage, grade 3 and grade 4, of newborn
					P52.3	Unspecified intraventricular (nontraumatic) hemorrhage of newborn
					P59.0	Neonatal jaundice associated with preterm delivery
					P61.2	Anemia of prematurity
					P77*	Necrotizing enterocolitis of newborn
					Q25.0	Patent ductus arteriosus

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
					O60.1***	Preterm labor with preterm delivery
Livebirths with MCM	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm) and through diagnosis codes in linked infants	Present/absent			See Table 10
Stillbirth	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis codes and procedures (based on data source pregnancy-identification algorithm)	Present/absent			See Table 10
SGA	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis codes	Present/absent			See Table 10
Gestational diabetes	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis codes	Present/absent			See Table 10
Gestational hypertension	All available data within 3 years before current pregnancy including date of conception	Defined through diagnosis codes	Present/absent			See Table 10

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
Health care utilization						
Number of office visits	Available data within 6 months before and including date of conception	Count of office visits	Number (0, 1, 2, ≥ 3)			Based on presence of evaluation and management codes associated with outpatient visits
Number of telemedicine encounters	Available data within 6 months before and including date of conception	Count of telemedicine encounters	Number (0, 1, 2, ≥ 3)			Based on the presence of codes for telemedicine visits as available
Number of ED visits	Available data within 6 months before and including date of conception	Count of ED visits	Number (0, 1, 2, ≥ 3)			Based on presence of evaluation and management codes associated with emergency department visits and place of service codes
Number of hospitalizations	Available data within 6 months before and including date of conception	Count of hospitalizations	Number (0, 1, 2, ≥ 3)			Based on revenue codes, place of service codes, and provider specialty
Characteristics of current pregnancy						
Multiple pregnancy	During pregnancy	Defined through diagnosis codes	Present/absent	ICD-10	O30*	Multiple gestation
					Z37.2*	Twins, both liveborn
					Z37.3*	Twins, one liveborn and one stillborn
					Z37.4*	Twins, both stillborn
					Z37.5*	Other multiple births, all liveborn
					Z37.6*	Other multiple births, some liveborn

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
TORCH infections	During pregnancy	Defined through diagnosis codes	Present/absent	ICD-10	B58*	Toxoplasmosis
					A50*	Congenital syphilis
					A51*	Early syphilis
					A52*	Late syphilis
					A53*	Other and unspecified syphilis
					A60*	Anogenital herpes viral [herpes simplex] infections
					A92.5	Zika virus disease
					B00*	Herpes viral [herpes simplex] infections
					B01*	Varicella [chicken pox]
					B02*	Zoster [herpes zoster]
					B34.3	Parvovirus infection, unspecified
					B97.6	Parvovirus as the cause of diseases classified elsewhere
					B08.3	Erythema infectiosum [fifth disease]
					B06*	Rubella {German measles]
					B25*	Cytomegaloviral disease
					B27.1*	Cytomegaloviral mononucleosis
					P35.0	Congenital rubella infection
					P35.1	Congenital cytomegalovirus infection
					P35.2	Congenital herpes viral [herpes simplex] infection
					P37.1	Congenital toxoplasmosis
SARS-CoV-2 infection	During pregnancy	Defined through diagnosis codes	Present/absent	ICD-10	U07.1	COVID-19

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
Comedications						
Teratogens (medications listed in Annex 3)	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, first trimester of pregnancy, or as indicated by relevant risk window	HICL		See Annex 3
Cannabinoids	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Cannabidiol
Preventive cluster headache drugs	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Verapamil, prednisone
Acute cluster headache drugs	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Sumatriptan, dihydroergotamine (intranasal forms)
Antidepressants	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Amitriptyline, bupropion, citalopram, duloxetine, fluoxetine, nefazodone, nortriptyline, paroxetine, sertraline, trazodone, venlafaxine
Antipsychotics	Available data within 6 months before and including date of	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Aripiprazole, haloperidol, olanzapine, paliperidone, quetiapine, risperidone

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
	conception and during pregnancy					
Oral antidiabetics	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Phenformin, metformin, buformin, glibenclamide, chlorpropamide, tolbutamide, glibornuride, tolazamide, carbutamide, glipizide, gliquidone, gliclazide, metahexamide, glisoxepide, glimepiride, acetohexamide, glymidine, phenformin and sulfonylureas, metformin and sulfonylureas, metformin and rosiglitazone, glimepiride and rosiglitazone, metformin and pioglitazone, glimepiride and pioglitazone, metformin and sitagliptin, metformin and vildagliptin, pioglitazone and alogliptin, metformin and saxagliptin, metformin and linagliptin, pioglitazone and sitagliptin, metformin and alogliptin, metformin and repaglinide, metformin and dapagliflozin, metformin and canagliflozin, metformin and acarbose, metformin and gemigliptin, linagliptin and empagliflozin, metformin and empagliflozin, saxagliptin and dapagliflozin, metformin and evogliptin, metformin and ertugliflozin,

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
						sitagliptin and ertugliflozin, acarbose, miglitol, voglibose, troglitazone, rosiglitazone, pioglitazone, sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, gemigliptin, evogliptin, sitagliptin and simvastatin, gemigliptin and rosuvastatin, exenatide, liraglutide, lixisenatide, albiglutide, dulaglutide, semaglutide, dapagliflozin, canagliflozin, empagliflozin, ertugliflozin, ipragliflozin, sotagliflozin, guar gum, repaglinide, nateglinide, pramlintide, benfluorex, mitiglinide, tolrestat
Insulin	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Insulins
				HCPCS	J1811	Insulin (Fiasp) for administration through DME (ie, insulin pump) per 50 units
					J1812	Insulin (Fiasp), per 5 units
					J1813	Insulin (Lyumjev) for administration through DME (ie, insulin pump) per 50 units
					J1814	Insulin (Lyumjev), per 5 units
					J1815	Injection, insulin, per 5 units
					J1817	Insulin for administration through DME (ie, insulin pump) per 50 units
Antihypertensive medications	Available data within 6 months before and	Defined through dispensed prescriptions	Present/absent pre-pregnancy,	HICL, HCPCS		Hypotensive agents

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
	including date of conception and during pregnancy		during pregnancy			
Lipid-lowering drugs	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Simvastatin, lovastatin, pravastatin, fluvastatin, atorvastatin, cerivastatin, rosuvastatin, pitavastatin, clofibrate, bezafibrate, aluminium clofibrate, gemfibrozil, fenofibrate, simfibrate, ronifibrate, ciprofibrate, etofibrate, clofibride, choline fenofibrate, colestyramine, colestipol, colextran, colesevelam, niceritrol, nicotinic acid, nicofuranose, aluminium nicotinate, nicotinyl alcohol (pyridylcarbinol), acipimox, nicotinic acid, combinations, dextrothyroxine, probucol, tiadenol, meglutol, omega magnesium pyridoxal 5, policosanol, ezetimibe, alipogene tiparvovec, mipomersen, lomitapide, evolocumab, alirocumab, bempedoic acid, inclisiran, lovastatin and nicotinic acid, simvastatin and ezetimibe, pravastatin and fenofibrate, simvastatin and fenofibrate, atorvastatin and ezetimibe, rosuvastatin and ezetimibe,

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
						rosuvastatin and omega, atorvastatin and omega, rosuvastatin and fenofibrate, bempedoic acid and ezetimibe, simvastatin and acetylsalicylic acid, pravastatin and acetylsalicylic acid, atorvastatin and amlodipine, simvastatin, acetylsalicylic acid and ramipril, rosuvastatin and acetylsalicylic acid, atorvastatin, acetylsalicylic acid and ramipril, rosuvastatin, amlodipine and lisinopril, atorvastatin and acetylsalicylic acid, rosuvastatin and amlodipine, rosuvastatin and valsartan atorvastatin, amlodipine and perindopril atorvastatin, acetylsalicylic acid and perindopril, rosuvastatin perindopril and indapamide, rosuvastatin amlodipine and perindopril, atorvastatin and perindopril, rosuvastatin and fimasartan, rosuvastatin and ramipril, atorvastatin amlodipine and ramipril
Antithyroid medications	Available data within 6 months before and including date of	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Methylthiouracil, propylthiouracil, benzylthiouracil, carbimazole, thiamazole, thiamazole,

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
	conception and during pregnancy					combinations, potassium perchlorate, diiodotyrosine, dibromotyrosine
Antiplatelet agents	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL, HCPCS		Ditazole, cloricromen, picotamide, clopidogrel, ticlopidine, acetylsalicylic acid, dipyridamole, carbasalate calcium, epoprostenol, indobufen, iloprost, abciximab, aloxiprin, eptifibatide, tirofiban, triflusal, beraprost, treprostinil, prasugrel, cilostazol, ticagrelor, cangrelor, vorapaxar, selexipag, combinations, acetylsalicylic acid, combinations with proton pump inhibitors
Anticoagulants	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL, HCPCS		Dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, ethyl biscoumacetate, clorindione, diphenadione, tioclomarol, fluindione, heparin, antithrombin III, dalteparin, enoxaparin, nadroparin, parnaparin, reviparin, danaparoid, tinzaparin, sulodexide, bemiparin, heparin combinations, streptokinase, alteplase, anistreplase, urokinase, fibrinolysin, brinase, reteplase, saruplase, ancrod, drotrecogin alfa (activated), Tenecteplase, protein C, desirudin, lepirudin, argatroban,

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
						melagatran, ximelagatran, bivalirudin, dabigatran etexilate, rivaroxaban, apixaban, edoxaban, betrixaban, defibrotide, dermatan sulfate, fondaparinux, caplacizumab
Anti-emetics and antinauseants	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, during pregnancy	HICL		Ondansetron, granisetron, tropisetron, dolasetron, palonosetron, palonosetron combinations, scopolamine, cerium oxalate, chlorobutanol, metopimazine, dronabinol, nabilone, aprepitant, casopitant, rolapitant, scopolamine combinations, chlorobutanol combinations, meclizine, tolazamide
Use of acute migraine medications (medications listed in Annex 2): triptans, ergotamine derivatives, prescription NSAIDs, acetaminophen, and opioids	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, and by trimester of pregnancy Number of users of each medication, number of different medications, number of dispensings, time (days) between dispensings,	HICL, HCPCS		See Annex 2

Table 12. Operational definitions of covariates

	Time window of ascertainment	Definition	Operational form	Code Type	Code	Description
			quantity dispensed			
Use of preventive migraine drugs (medications listed in Annex 2): topiramate, anti-epileptics, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitor, and botulin toxin	Available data within 6 months before and including date of conception and during pregnancy	Defined through dispensed prescriptions	Present/absent pre-pregnancy, and by trimester of pregnancy Number of users of each medication, number of different medications, number of dispensings, time (days) between dispensings, quantity dispensed	HICL, HCPCS		See Annex 2

Abbreviations: CMV, cytomegalovirus; ED, emergency department; HICL, hierarchical ingredient code list; ; MCM, major congenital malformation; NSAID, nonsteroidal anti-inflammatory drug; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SGA, small for gestational age; TORCH infections, toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus (CMV), herpes simplex, and Zika virus disease; US, United States

Note: HICL codes are proprietary to First Databank. The list of medications will be updated as new medications are approved over the course of the study. Updates will be made before each annual interim analysis.

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

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

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

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