NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	Observational Cohort Study of Safety of Etrasimod During Pregnancy in US Claims Databases
Protocol number	C5041042
Protocol version identifier	Version 3.0
Date	23 March 2026
Active substance	Etrasimod, ATC Code L04AE05
Medicinal product	VELSIPITY®
Research question and objectives	Research question: Is there an increased risk of adverse pregnancy and/or infant outcomes in individuals who are exposed to etrasimod during pregnancy? Primary objective: Describe the prevalence of major congenital malformations (MCMs) in infants born alive to pregnant individuals with a diagnosis of ulcerative colitis (UC) who are (1) exposed to etrasimod during pregnancy (Etrasimod Cohort) and (2) unexposed to etrasimod but exposed to other advanced UC treatments during pregnancy (Other Advanced UC Treatments Cohort) and compare the prevalence between cohorts if sample size permits Secondary objective: Describe the prevalence of pregnancy (spontaneous abortion, pregnancy termination, gestational hypertension, pre-eclampsia, eclampsia, and stillbirth) and infant (preterm birth and small for gestational age) outcomes among individuals in the Etrasimod Cohort and the Other Advanced UC Treatments Cohort and compare the prevalence between cohorts if sample size permits
Country(ies) of study	United States
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
ACOG	American College of Obstetricians and Gynecologists
AE	Adverse event
AEM	Adverse event monitoring
ATT	Average treatment effect in the treated
BMI	Body mass index
CD	Crohn's disease
CI	Confidence interval
CMS	Centers for Medicare & Medicaid Services
CPT®	Common Procedural Terminology
DAPI	Dynamic Assessment of Pregnancies and Infants
DCT	Data collection tool
EC	Ethics committee
EDC	Estimated date of conception
EHR	Electronic health records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EOP	End of pregnancy
FDA	Food and Drug Administration
GPI	Generic Product Identifier

Abbreviation	Definition
GPP	Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HIRD	Healthcare Integrated Research Database
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases Procedure Coding System, Tenth Revision
IHD	Instant Health Data
IL	Interleukin
IPT	Inverse probability of treatment
IPTW	Inverse probability of treatment weighting
ISPE	International Society of Pharmacoepidemiology
IRB	Institutional review board
JAK	Janus kinase
LMP	Last menstrual period
mAB	Monoclonal antibody
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
mm Hg	Millimeters of mercury
NDC	National Drug Code
NIPT	Non-invasive prenatal testing
NIS	Non-interventional study

Abbreviation	Definition
ORD	Optum Research Database
PASS	Post-authorization safety study
PPV	Positive predictive value
S1P	Sphingosine-1-phosphate
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SGA	Small for gestational age
SOP	Standard operating procedure
TNF	Tumor necrosis factor
TORCH	Toxoplasmosis, other infections, rubella, cytomegalovirus, herpes simplex virus, and Zika virus disease
UB	Universal billing
UC	Ulcerative colitis
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 Safety of Etrasimod During Pregnancy in US Claims Databases
  - Version 3.0, 23 March 2026
  - Authors: Shahar Shmuel, Pfizer, Inc.; Bora Plaku, Optum Epidemiology; Jessica Franklin, Optum Epidemiology; Maria Van Rompay, Carelon Research; Stephan Lanes, Carelon Research
- **Rationale and background:** Etrasimod is an oral, once-daily sphingosine-1-phosphate receptor modulator that was approved by the United States (US) Food and Drug Administration (FDA) on 12 October 2023 for the treatment of moderately to severely active ulcerative colitis (UC). There are limited data on the safety of etrasimod during pregnancy. This non-interventional study is designated as a post-authorization safety study and will fulfill an FDA post-marketing requirement to assess the safety of etrasimod in pregnant individuals.
- **Research question and objectives:**
  - Research question: Is there an increased risk of adverse pregnancy and/or infant outcomes in individuals who are exposed to etrasimod during pregnancy?
  - Primary objective: Describe the prevalence of major congenital malformations (MCMs) in infants born alive to pregnant individuals with a diagnosis of UC who are (1) exposed to etrasimod during pregnancy (Etrasimod Cohort) and (2) unexposed to etrasimod but exposed to other advanced UC treatments during pregnancy (Other Advanced UC Treatments Cohort) and compare the prevalence between cohorts if sample size permits
  - Secondary objective: Describe the prevalence of pregnancy (spontaneous abortion, pregnancy termination, gestational hypertension, pre-eclampsia, eclampsia, and stillbirth) and infant (preterm birth and small for gestational age) outcomes among individuals in the Etrasimod Cohort and the Other Advanced UC Treatments Cohort and compare the prevalence between cohorts if sample size permits
- **Study design:** This is an observational cohort study that will be conducted within two US-based health insurance claims databases. The prevalence of the study outcomes will be described among cohorts of individuals with UC who are exposed to etrasimod during pregnancy or who are unexposed to etrasimod but are exposed to other advanced UC treatments during pregnancy.
- **Population:** The study population will consist of pregnant individuals with UC and an estimated date of conception between 5 January 2023 and 30 September 2028 (with outcomes observed through 30 September 2029) who were exposed to etrasimod or other advanced UC treatments during pregnancy.

- **Variables:** Exposure to etrasimod and comparator treatments will be identified by claims for drug dispensings or administrations. Diagnoses of UC will be identified by the presence of at least one diagnosis code for UC between six months prior to pregnancy and the end of pregnancy. Study outcomes will be identified using claims-based algorithms, and the primary outcome of MCMs will be restricted to outcomes confirmed via medical record review. All covariate information will be identified using claims data, including risk factors for the study outcomes, predictors of treatment choices, and demographics.
- **Data sources:** This study will use data from the Optum Research Database (ORD) and the Healthcare Integrated Research Database (HIRD), which contain eligibility and medical and pharmacy claims from large US health plans. The individuals covered by these plans are geographically diverse across the US.
- **Study size:** If we were to assume complete case ascertainment in the primary analysis, the target size for the study would be 408 etrasimod-exposed pregnancies (expected to yield approximately 214 etrasimod-exposed pregnancies with linked liveborn infants), which will be matched 1:4 to the comparator group, for a total of 1,632 comparator pregnancies. This target size would provide an estimated 80% power to detect a prevalence ratio of 2.5 for the primary outcome of MCM among linked liveborn infants and could be achieved with approximately 82 etrasimod-exposed pregnancies per year for five years across the two data sources. However, because only 30-40% of patients are eligible for medical record procurement and confirmation of the outcome, the power of the primary analysis is expected to be 40-48%. Secondary analyses utilizing all potential MCMs identified in claims will have greater power.
- **Data analysis:** One interim report will describe accrual of eligible patients into each of the study cohorts. The interim report will also describe each cohort according to key characteristics and outcome counts. The final report will provide the same cohort descriptions, as well as the prevalence of each study outcome by cohort. If sample size permits, the final report will also include a comparative analysis utilizing inverse probability of treatment weighting that estimates the relative prevalence of each of the study outcomes, with the primary analysis of MCMs restricted to cases confirmed by medical record review. All analyses will be conducted and reported separately by data source, and a meta-analysis combining results across databases will also be performed.

Milestones: The planned milestones for submission to the FDA are the draft protocol on 31 May 2024, the final protocol on 28 February 2025, the interim report on 30 November 2027, and the final report on 31 March 2032.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1.0	28 February 2025	Substantial	4.0; 9.1; 9.2.1; 9.2.4; 9.2.6.1; 9.2.7; 9.2.8; 9.3.1; 9.3.3; 9.7.4	Changed the definition of the start of pregnancy from last menstrual period to estimated date of conception	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	9.3.2.1	Specified that all available potential MCM cases will be reviewed and that those with insufficient clinical detail to determine case status will be classified as such	FDA comments 14 November 2024
1.0	28 February 2025	Administrative	9.7.2.3	Corrected a typo that erroneously referred to Table 3 to instead refer to Table 4	Correction / FDA comments 14 November 2024
1.0	28 February 2025	Substantial	9.7.2.3	Clarified that confounders identified during the study that are strongly associated with etrasimod use and pregnancy/infant outcomes may also be included in the outcome regression models	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	9.7.2.3	Clarified that potential stratification variables will first be evaluated for use as stratification variables	FDA comments 14 November 2024

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1.0	28 February 2025	Substantial	9.2.1	Changed the age range for study inclusion from 18-49 to 18-50	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	9.3.2.1; Annex 3	Updated definition of major congenital malformations to include only the Metropolitan Atlanta Congenital Defects Program	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	9.3.3	Updated covariate list to include additional concurrent maternal medical conditions	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	9.3.2	Added eclampsia, pre-eclampsia, and pregnancy termination as secondary outcomes	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	Annex 2	Aligned the list of teratogens with the pregnancy registry study and removed dolutegravir from the list of teratogens	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	9.7.1	Added a description of a summary table that will be used to describe UC treatment patterns within the study cohorts	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	Table 4	Updated denominator definitions for consistency with the registry study	FDA comments 14 November 2024

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1.0	28 February 2025	Substantial	Table 5	Updated reference estimates for consistency with the registry study	FDA comments 14 November 2024
1.0	28 February 2025	Substantial	Table 5	Added sample size calculations assuming matching ratios of 1:2 and 1:3	FDA comments 14 November 2024
1.0	28 February 2025	Non-substantial	Abstract; 9.5	Updated study size language to improve clarity	Clarification
2.0	01 August 2025	Substantial	9.2.1; 9.7.2.3; 9.7.4	Expanded eligible age range from 18-50 years at EDC to 15-50 years at EDC; added a subgroup analysis stratifying by age 18-50 vs. < 18 years; amended propensity score modeling and matching to account for stratified analyses.	FDA Comments 18 June 2025
2.0	01 August 2025	Substantial	9.4.3	Clarified why only 30-40% of MCM patients are eligible for medical record procurement and adjudication.	FDA Comments 18 June 2025
2.0	01 August 2025	Substantial	9.5; Table 5	Updated background prevalence of preterm birth based on most recent data; updated accompanying sample size calculations	FDA Comments 18 June 2025

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	01 August 2025	Substantial	Table 5	Added footnote (*) containing details of the test and software used in sample size calculations	FDA Comments 18 June 2025
2.0	01 August 2025	Non-substantial	Study Design; 9.1	Clarified that infant outcome ascertainment would be extended for up to one year after birth	Clarification
2.0	01 August 2025	Substantial	9.2.1; 9.2.2	Clarified the scenarios under which patients with dual exposure to etrasimod and other advanced UC treatment would be excluded *a priori.*	Clarification
2.0	01 August 2025	Non-substantial	9.2.2	Added, “In the analysis of MCMs, pregnancies meeting the following criteria are excluded” in order to improve flow.	Cosmetic change
2.0	01 August 2025	Substantial	9.2.3	Clarified that the infants of the last accrued pregnancies will have at least 3 months of follow-up for MCM assessment.	Correction / clarification
2.0	01 August 2025	Non-substantial	9.2.4	Made minor edits to wording (removed “that”, “ORD” and “HIRD”; replaced “last menstrual period” with “LMP”)	Cosmetic changes

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	01 August 2025	Substantial	9.2.6.1; 9.2.6.2	Added details to cohort assignment procedures	Clarification
2.0	01 August 2025	Non-substantial	9.2.6.2	Clarified that the list of approved medications for the treatment of moderate to severe UC would be reviewed before each report	Clarification
2.0	01 August 2025	Substantial	9.2.8	Added further detail to censoring criteria	Clarification
2.0	01 August 2025	Non-substantial	9.3.1.1	Made minor wording additions and deletions to improve clarity and flow; added a note on logically inconsistent days' supply values.	Cosmetic changes; clarifications
2.0	01 August 2025	Substantial	9.3.1.2	Added a coding system for identifying etrasimod dispensings (i.e., GPI)	Correction
2.0	01 August 2025	Non-substantial	9.3.2	Defined "ORD" abbreviation	Clarification
2.0	01 August 2025	Non-substantial	9.3.2.1	Added names for claims-based MCM algorithms ("Algorithm A", "Algorithm B")	Cosmetic change
2.0	01 August 2025	Substantial	9.3.2.1	Clarified handling of medical records with insufficient clinical detail; clarified validation procedures for	Clarifications

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				Algorithms A and B	
2.0	01 August 2025	Non-substantial	9.3.2.1	Removed description of a sensitivity analysis already discussed in Section 9.7.4	Eliminate redundancy
2.0	01 August 2025	Substantial	9.3.2.1	Added detail on describing follow-up among linked infants	Clarification
2.0	01 August 2025	Substantial	9.3.2.8	Added more details to preterm birth primary and sensitivity analyses.	Clarification
2.0	01 August 2025	Substantial	Table 4, 9.3.2.4, 9.3.2.5, 9.3.2.6	Amended denominator for stillbirth and added sensitivity analyses regarding the choice of denominator for pre-eclampsia, eclampsia, and stillbirth	Correction.
2.0	01 August 2025	Substantial	Table 4	Removed description of censoring criteria from MCM and SGA outcome ascertainment windows, for consistency with other outcome ascertainment windows; added footnotes referencing censoring criteria.	Correction
2.0	01 August 2025	Substantial	9.3.3	Clarified that baseline covariates would include year of EDC rather than month and year, that reproductive	Corrections

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				history “up to” two years prior to EDC would be included, and that empirical covariates would also be evaluated by exposure window; added NIPT and substance-use diagnoses to covariates; removed qualifiers for depression and anxiety	
2.0	01 August 2025	Non-substantial	9.4.2	Replaced “Generic Product Identifier” with “GPI”	Cosmetic
2.0	01 August 2025	Substantial	9.4.2.1	Clarified assumptions regarding patients who do vs. do not disenroll in the HIRD	Clarification
2.0	01 August 2025	Substantial	Table 5	Moved footnote (**) from pre-eclampsia to MCM	Correction
2.0	01 August 2025	Substantial	9.7.1	Further clarified contents of interim report; removed details on variable reporting addressed in the statistical analysis plan	Correction/ clarification
2.0	01 August 2025	Non-substantial	9.7.2.1	Eliminated redundant language pertaining to PPV and sensitivity for Algorithms A and B	Consistency with statistical analysis plan

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
2.0	01 August 2025	Substantial	9.7.2.2	Replaced flow diagram with attrition table; added further detail on summarizing use patterns	Correction/clarification
2.0	01 August 2025	Substantial	9.7.2.3	Added further details on propensity score modeling and matching in the final comparative analysis	Clarification
2.0	01 August 2025	Non-substantial	9.7.2.3	Removed redundant wording on adjusting comparative estimates of claims-defined MCMs based on PPVs and sensitivities of MCM algorithms	Consistency with statistical analysis plan
2.0	01 August 2025	Non-substantial	9.7.2.4	Tweaked wording of IPTW/propensity score modeling description for clarity, flow, and consistency with statistical analysis plan	Consistency with statistical analysis plan
2.0	01 August 2025	Substantial	9.7.4	Reordered and expanded upon additional analyses for consistency with statistical analysis plan	Consistency with statistical analysis plan
3.0	23 March 2026	Substantial	Throughout	Added gestational hypertension to the secondary study outcomes	FDA request
3.0	23 March 2026	Non-substantial	9.3.2.8	Added clarification that	Consistency with Table 4.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				SGA analysis would be restricted to singleton pregnancies and their liveborn linked infants	
3.0	23 March 2026	Non-substantial	Table 5	Added footnote clarifying required pregnancies for MCM, SGA and preterm birth	Clarification
3.0	23 March 2026	Substantial	9.9	Added limitations regarding 1) estimation of prevalences of gestational hypertension, pre-eclampsia, eclampsia and stillbirth; 2) prevalence-based focus; and 3) non-sequential study design	Clarification
3.0	23 March 2026	Substantial	6.0	Added clarifying footnote on end of data collection to milestones table	Clarity
3.0	23 March 2026	Non-substantial	9.2.5	Removed information about algorithms not used for this study to prevent confusion	Clarity
3.0	23 March 2026	Substantial	9.2.8	Clarified censoring criteria for infant outcomes	Clarity
3.0	23 March 2026	Non-substantial	9.3.2.1.1	Reiterated proportion of study participants for whom medical records can be requested	Consistency with other parts of the protocol
3.0	23 March 2026	Substantial	9.4.2; 9.4.2.1	Updated information on	Update

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				HIRD; provided references	
3.0	23 March 2026	Non-substantial	Throughout	Minor changes in wording	Editorial

6. MILESTONES

Milestone	Planned Date
Draft protocol submission	31 May 2024
Final protocol submission	28 February 2025
Start of data collection[1]	17 November 2026
End of data collection[2]	31 May 2031
Interim report	30 November 2027
Final study report	31 March 2032

1 Start of data collection for secondary database studies is the date of data extraction for the interim report
2 Date on which the analytical dataset will first be completely available. The analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s). Therefore, this is the date at which chart retrieval is complete and all outcomes are adjudicated, allowing the statistical analysis to proceed.

7. RATIONALE AND BACKGROUND

Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by periods of active inflammation and ulcers in the mucosa of the colon and rectum alternating with periods of clinical remission (Ungaro et al., 2017; Cohen & Stein, 2023). Disease onset typically occurs between the ages of 30 and 40, and prevalence in the United States (US) is approximately 214 cases per 100,000 people (Ungaro et al. 2017). In clinical practice, moderate UC is often defined as patients with no or minimal signs of systemic toxicity (Cohen & Stein, 2023). These patients typically have frequent (four to six per day) loose, bloody stools; mild anemia; and mild to moderate abdominal pain (Cohen & Stein, 2023). Severe UC is typically defined as at least six loose, bloody stools per day accompanied by severe cramps and evidence of systemic toxicity, which may include fever, tachycardia, anemia, or elevated C-reactive protein and/or erythrocyte sedimentation rate (Cohen & Stein, 2023).

For patients with active UC, the treatment goal is to achieve steroid-free remission (Dassopoulos et al., 2015; Rubin et al., 2019). There are multiple therapeutic classes available to treat UC, with therapies being classified as induction therapies or maintenance therapies (Cohen & Stein, 2023). Induction therapies are those with relatively rapid onset of action, while maintenance therapies may have a longer onset but be more appropriate for long-term use, and some drugs may be used for both induction and maintenance of remission (Cohen & Stein, 2023). Current maintenance therapies approved by the US Food and Drug Administration (FDA) for the treatment of moderate to severe UC include the anti-

tumor necrosis factor (TNF) monoclonal antibodies (mAB) adalimumab, golimumab, and infliximab; the Janus kinase (JAK) inhibitors tofacitinib and upadacitinib; the interleukin-12 and -23 (IL-12/23) antagonists mirikizumab, ustekinumab, and vedolizumab; and the sphingosine-1-phosphate (S1P) receptor modulators ozanimod and etrasimod (Cohen & Stein, 2023; FDA, 2023b).

Etrasimod is an oral, once-daily, S1P receptor modulator that was approved by the US FDA for the treatment of moderately to severely active UC on 12 October 2023 (FDA, 2023b). This is currently the only FDA-approved indication for etrasimod. In Phase 3 trials, a greater proportion of patients receiving etrasimod achieved clinical remission of UC after 52 weeks of treatment compared to patients receiving placebo (Sandborn et al., 2023). However, there are limited data on the safety of etrasimod during pregnancy. In animal studies, embryofetal toxicity was observed in rats and rabbits administered etrasimod at clinically relevant doses (FDA, 2023a). The FDA label for etrasimod states that individuals of childbearing potential should use effective contraception while on the treatment, as well as for one week after stopping etrasimod (Velsipity package insert, 2023). Thus, the purpose of this study is to evaluate the safety of etrasimod during pregnancy with regard to prevalence of pregnancy and/or infant outcomes, including major congenital malformations (MCMs), spontaneous abortion, pregnancy termination, gestational hypertension, pre-eclampsia, eclampsia, stillbirth, preterm birth, and small for gestational age (SGA).

This non-interventional study (NIS) is designated as a post-authorization safety study (PASS) and is a commitment to the US FDA.

8. RESEARCH QUESTION AND OBJECTIVES

Research question: Is there an increased risk of adverse pregnancy and/or infant outcomes in individuals who are exposed to etrasimod during pregnancy?

Primary objective: Describe the prevalence of MCMs in infants born alive to pregnant individuals with a diagnosis of UC who are (1) exposed to etrasimod during pregnancy (Etrasimod Cohort) and (2) unexposed to etrasimod but exposed to other advanced UC treatments during pregnancy (Other Advanced UC Treatments Cohort) and compare the prevalence between cohorts if sample size permits

Secondary objective: Describe the prevalence of pregnancy (spontaneous abortion, pregnancy termination, gestational hypertension, pre-eclampsia, eclampsia, and stillbirth) and infant (preterm birth and SGA) outcomes among individuals in the Etrasimod Cohort and the Other Advanced UC Treatments Cohort and compare the prevalence between cohorts if sample size permits

9. RESEARCH METHODS

9.1. Study Design

This is an observational cohort study using two US-based administrative healthcare claims databases, each of which will be used to identify pregnancy episodes among individuals with UC who are exposed to etrasimod during pregnancy or who are unexposed to etrasimod but exposed to other advanced UC treatments during pregnancy.

This study will accrue pregnancy episodes that begin between 5 January 2023, 40 weeks prior to the date of etrasimod approval in the US, and 30 September 2028, with outcomes

being observed through 30 September 2029. The subset of individuals whose pregnancy outcome is a live birth will be linked to their infants to the extent possible, to extend infant outcome ascertainment for up to one year after birth. More information on linkage can be found in 9.4.1.1 and 9.4.2.1. The primary outcome is MCMs, for which two claims-based algorithms will be validated via medical record review. The secondary outcomes are spontaneous abortion, pregnancy termination, gestational hypertension, pre-eclampsia, eclampsia, stillbirth, preterm birth, and SGA, which will be identified from claims data without medical record review. The primary analysis will describe the prevalence of each outcome in the Etrasimod Cohort and the Other Advanced UC Treatments Cohort, and, if sample size permits, the relative prevalence between the groups will be compared using inverse probability of treatment weighting (IPTW) to adjust for potential confounding. For the final report and prior to the first round of medical record procurement, patients in the Etrasimod Cohort will be matched 1:4 to patients in the comparator group based on age (± 2 years) at estimated date of conception (EDC) and calendar year of EDC. Matching and weighting will not be performed in the interim report.

9.2. Setting

All qualifying pregnancies during the study period within two US-based health insurance claims databases among individuals with UC who are exposed to etrasimod during pregnancy or individuals with UC who are not exposed to etrasimod but who are exposed to other advanced UC treatments during pregnancy will be included.

9.2.1. Inclusion Criteria

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

1. Exposure to etrasimod or to other advanced UC treatments during a given exposure window (Section 9.2.6 and Section 9.3.1.1)
2. Meet criteria for diagnosis of UC (Section 9.2.5)
3. Age 15-50 at EDC (Section 9.2.4)
4. EDC falls within the study period (5 January 2023 – 30 September 2028)
5. Continuous health plan enrollment with medical and pharmacy benefits for a minimum of six months prior to and including the EDC
6. For analyses of study outcomes, an observed end-of-pregnancy outcome (i.e., live birth, stillbirth, spontaneous abortion or pregnancy termination)

9.2.2. Exclusion Criteria

Individuals with exposure to both etrasimod and other advanced UC treatments during the first trimester of pregnancy will be excluded from all analyses.

MCM analyses will be restricted to pregnancies without known teratogen exposure, pregnancies without infections known to cause anomalies, and to infants without chromosomal anomalies. Pregnancies excluded from the MCM analyses for meeting any of the following criteria may still be included in the analyses of the secondary outcomes (e.g., pregnancy episodes excluded from the analysis of MCMs due to first-trimester exposure to methotrexate, an immunomodulator used to treat UC, may be included in the

analyses of spontaneous abortion, pregnancy termination, gestational hypertension, pre-eclampsia, eclampsia, stillbirth, preterm birth, and SGA).

In the analysis of MCMs, pregnancies meeting the following criteria will be excluded:

1. Pregnancy episodes that have been exposed to known teratogens
    - ANNEX 2 provides a list of known teratogens, their associated half-lives, and relevant exposure windows
2. Pregnancy episodes with infections known to cause congenital anomalies during pregnancy
    - TORCH infections, which consist of toxoplasmosis, other infections (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, herpes simplex virus, and Zika virus disease
3. Pregnancy episodes resulting in infants with syndromic or chromosomal anomalies identified during pregnancy or at birth
    - Chromosomal trisomies (e.g., Down syndrome, Edwards syndrome); monosomies and deletions from the autosomes; balanced rearrangements and structural markers; Turner's syndrome or other abnormalities of the sex chromosomes; and other chromosomal abnormalities

9.2.3. Study Period

The study period will begin on 5 January 2023, which is 40 weeks prior to the day that the US FDA approved etrasimod in the US. This will allow individuals who are already pregnant at the time of etrasimod approval to be included in the study if they become exposed later in their pregnancy; this timing allows for the inclusion of pregnancy gestations up to 42 weeks since last menstrual period (LMP). Accrual will end on 30 September 2028, with outcomes being observed through 30 September 2029, the end of the study period. This will allow all accrued pregnancies time to complete, with at least 3 months for the linked infants of last accrued pregnancies to be assessed with respect to the MCM outcome. The study may end earlier if the required sample size is achieved by the time of the interim report.

9.2.4. Pregnancy Identification and Estimation of Date of Conception

Briefly, pregnancies will be identified based on the presence of International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) pregnancy codes. Z3A codes denote weeks of gestation at the time of the encounter; for example, Z3A.20 denotes a patient at 20 weeks' gestation at the time of the encounter, and Z3A.25 denotes a patient at 25 weeks' gestation at the time of the encounter. Pregnancies are identified via Z3A codes and/or pregnancy outcome codes (e.g., spontaneous abortion, stillbirth) that will include ICD-10-CM diagnosis or procedure codes, Current Procedural Terminology (CPT®[1]) codes,

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and Healthcare Common Procedure Coding System (HCPCS) codes. Additional details regarding pregnancy identification are provided in Sections 9.4.1.1 and 9.4.2.1.

The start of pregnancy will be defined as the EDC, which is defined as the estimated date of LMP (i.e., the first day of the last menstrual period before pregnancy) plus 14 days; the start of the exposure window is defined as the EDC minus at least five times the therapy-specific half-life (Sections 9.3.1.2 and 9.3.1.3). Validation of LMP estimation using Z3A codes has indicated good performance, with a median difference in days between LMP date based on Z3A codes and adjudicated LMP date from the medical record of 4.0 days (interquartile range: 2.0–10.0 days) (Chomistek et al., 2023). Gestational age and trimester definitions are anchored by the LMP date, whereby, for example, 12 weeks' gestation is considered 12 completed weeks after LMP.

The end of pregnancy will be defined as the date of an end-of-pregnancy outcome (i.e., spontaneous abortion, livebirth, stillbirth or pregnancy termination). The date and type of the outcome will be determined by diagnosis and procedure codes observed. A definition of the time periods of pregnancy can be found in Table 1.

Table 1. Definition of pregnancy time periods

Time period	Start of time period	End of time period
LMP	0 weeks$^{0/7\ days}$	Not applicable
EDC	2 weeks$^{0/7\ days}$	Not applicable
First trimester[a,b]	EDC	13 weeks$^{6/7\ days}$
Second trimester[a,b]	14 weeks$^{0/7\ days}$	27 weeks$^{6/7\ days}$
Third trimester[1]	28 weeks$^{0/7\ days}$	End-of-pregnancy outcome
Pregnancy period	EDC	End-of-pregnancy outcome

Abbreviations: EDC, estimated date of conception; LMP, last menstrual period
a Calculated in weeks since LMP (ACOG, 2024)
b End of the time period is the end of time period shown or the date of pregnancy outcome, whichever is sooner

9.2.5. Identification of UC

Individuals will be considered to have UC if they have at least one ICD-10-CM diagnosis code in any position for UC (K51***) between six months prior to pregnancy and the end of pregnancy.
Alternate definitions of UC may be considered if validated, well-performing ICD-10-CM algorithms from similar study populations are published during the study period.

9.2.6. Study Cohorts

9.2.6.1. Etrasimod Cohort

The Etrasimod Cohort will include all pregnancy episodes with a diagnosis of UC (Section 9.2.5) and at least one dispensing of etrasimod as their first study drug exposure during the relevant exposure window. Patients in this cohort may also be exposed to conventional UC treatments such as 5-aminosalicylic acids (5-ASAs), systemic

glucocorticoids, and immunomodulators. If an individual contributes more than one pregnancy episode, exposure will be evaluated separately for each pregnancy.

9.2.6.2. Other Advanced UC Treatments Cohort

The Other Advanced UC Treatments Cohort will include all pregnant individuals with a diagnosis of UC (Section 9.2.5) and at least one dispensing of other select advanced UC treatments as their first study drug exposure during the treatment-specific exposure windows (Table 3). Patients in this cohort may also be exposed to conventional UC treatments. If an individual contributes more than one pregnancy episode, exposure will be evaluated separately for each pregnancy.

The other advanced treatments used to define this cohort are as follows:

- Adalimumab
- Golimumab
- Infliximab
- Tofacitinib
- Upadacitinib
- Mirikizumab
- Ustekinumab
- Vedolizumab
- Ozanimod

The list of approved medications for the treatment of moderate to severe UC will be reviewed before each report for completeness and updated as new codes and/or treatments become available.

9.2.7. Baseline Period

The baseline period will include a minimum of six months of continuous enrollment prior to and including the EDC, and this is required for study eligibility (Section 9.2.1). Select covariates will be captured using all available data up to two years prior to and including the EDC (Section 9.3.3). Requiring a minimum of six months of continuous enrollment will exclude some otherwise eligible patients with shorter periods of enrollment; however, a longer baseline period allows for better capture of covariate information, including diagnoses prior to the start of pregnancy.

9.2.8. Outcome Ascertainment Period

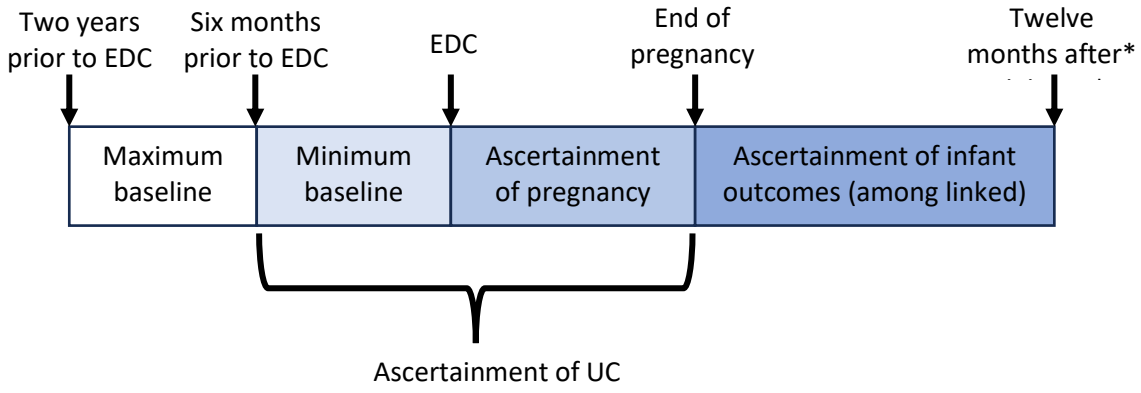
To assess occurrence of the relevant pregnancy-related outcomes, pregnancy episodes will be followed from the EDC through the soonest of 1) occurrence of the relevant pregnancy outcome (i.e., spontaneous abortion, pregnancy termination, gestational hypertension, pre-eclampsia, eclampsia, or stillbirth); 2) a switch to another cohort-defining medication within the relevant exposure window (i.e., a switch from etrasimod to another advanced UC treatment listed in Section 9.2.6.2, or vice-versa); 3) the end of pregnancy (by livebirth or fetal death); 4) maternal death; 5) maternal disenrollment from the health plan; 6) the end of

the outcome ascertainment window (Table 4); 7) the end of the study period, or 8) 42 weeks of gestation (since LMP).

Infant outcomes will be assessed among the subset of pregnancies resulting in livebirths during enrollment that are linked to the pregnant individual's data. MCM will be ascertained among linked infants between birth and the earliest of 1) occurrence of the outcome; 2) death; 3) disenrollment from the health plan; 4) 12 months of age or 5) the end of the study period. However, infants born near the end of the study period may not have a full 12 months in which to ascertain MCM. SGA and preterm birth will be ascertained among linked infants between EDC and the earliest of 1) occurrence of each outcome; 2) a switch to another cohort-defining medication within the exposure window; 3) death; 4) disenrollment from the health plan; 5) 30 days after delivery (for SGA).

A study timeline depicting the study periods is shown in Figure 1.

Figure 1. Study timeline for the primary analysis



Abbreviations: EDC, estimated date of conception; UC, ulcerative colitis
* Or end of study period

The censoring criteria defined above work together with the final inclusion criteria requiring an observed end-of-pregnancy outcome (Section 9.2.1) to determine the analysis sample for each outcome. For example, all pregnancies censored prior to the observation of gestational hypertension, pre-eclampsia or eclampsia are dropped from the analysis of these study outcomes. This implies that pregnant individuals who switch therapy (i.e., have dual exposure) prior to the occurrence of these study outcomes (or prior to the end of pregnancy for pregnancies that do not have an occurrence of these outcomes) will be dropped from the analysis of these outcomes. Similarly, pregnancies censored prior to the end of pregnancy are dropped from the analysis of study outcomes that occur at or after the end of pregnancy (spontaneous abortion, pregnancy termination, stillbirth, preterm birth, SGA, MCM). For all these study outcomes except MCM, pregnant individuals with dual exposure or switching during pregnancy will be dropped from analyses. For MCMs, dual exposure during the first trimester exposure window is an exclusion criterion (Section 9.2.2).

9.3. Variables

9.3.1. Exposures

9.3.1.1. Exposure Windows

Eligible pregnancies will be classified as exposed if they had any eligible exposure in the relevant window to etrasimod (Etrasimod Cohort) or other advanced UC treatment(s) (Other Advanced UC Treatments Cohort) (Section 9.2.6). As different treatments have different rates of elimination, the start of each relevant exposure window will extend backwards in time (prior to the EDC) by a corresponding therapy-specific window, which is based on the time to non-detectable concentration in the body (defined as at least five times the clearance half-life, rounded up to the next whole day). This ensures the capture of exposure to UC treatments administered or dispensed prior to the EDC but that remain in the body at EDC (Sections 9.3.1.2 and 9.3.1.3). The following exposure window end dates will be identified (all with the same start date of EDC minus at least five times the therapy-specific half-life):

- First trimester exposure window
  - End date: End of the first trimester (13 weeks$^{6/7\ days}$) or the end of pregnancy, whichever is sooner
- 20-week exposure window
  - End date: End of the 20th week of gestation (19 weeks$^{6/7\ days}$) or the end of pregnancy, whichever is sooner
- 37-week exposure window
  - End date: End of the 37th week of gestation (36 weeks$^{6/7\ days}$) or the end of pregnancy, whichever is sooner
- Pregnancy exposure window
  - End date: End of pregnancy

For primary analyses, the defined exposure window will vary by study outcome, according to its relevant etiologic period, as shown in Table 2.

Table 2. Timing of exposure assessment for primary analyses of study outcomes

Outcome	Exposure Window
Major congenital malformations	First trimester exposure window
Spontaneous abortion	20-week exposure window
Pregnancy termination	Pregnancy exposure window
Gestational hypertension	Pregnancy exposure window
Pre-eclampsia	Pregnancy exposure window
Eclampsia	Pregnancy exposure window
Stillbirth	Pregnancy exposure window
Preterm birth	37-week exposure window

Table 2. Timing of exposure assessment for primary analyses of study outcomes

Small for gestational age	Pregnancy exposure window

Duration of exposure for dispensed oral medications will further incorporate the documented days' supply, which is typically captured in pharmacy claims data. In cases where days' supply is missing or where the value of days' supply is out-of-range or logically inconsistent (e.g., a very large days' supply), it will be imputed using mean days' supply for the medication observed in the eligible study population. A pregnancy will be considered exposed to an oral medication during a given exposure window if the dispensing date plus the days' supply overlaps with the therapy-specific exposure window; for injections and infusions, a pregnancy will be considered exposed during a given exposure window if the administration date overlaps with the therapy-specific exposure window.

9.3.1.2. Etrasimod

Etrasimod dispensings will be identified by National Drug Codes (NDC) or Generic Product Identifier (GPI) codes. The list of NDCs used to identify etrasimod (VELSIPITY®) will be updated prior to each data pull. The elimination half-life of etrasimod is approximately 30 hours (FDA, 2023a); therefore, the start of the exposure window will be extended backwards from the EDC by seven days, which is equal to at least five times the elimination half-life of etrasimod. For example, a patient dispensed a 30-day supply of etrasimod would be eligible for inclusion in the study if they received a dispensing between 37 days prior to the EDC and the end of pregnancy.

9.3.1.3. Comparator UC Treatments

Dispensings or administrations of comparator drugs that define the Other Advanced UC Cohort will be identified through a combination of NDCs and HCPCS codes, lists of which will be periodically reviewed throughout the course of the study and updated as necessary. The start of the exposure window will be extended backwards from the EDC by a period equal to at least five times the elimination half-life, as detailed in Table 3.

Table 3. Exposure windows of each advanced UC comparator medication

Comparator treatment	Elimination half-life[a]	Start of exposure window
Adalimumab	14 days (Humira package insert, 2012)	EDC – 70 days
Golimumab	14 days (Simponi package insert, 2013)	EDC – 70 days
Infliximab	8–9.5 days (Remicade package insert, 2021)	EDC – 48 days
Tofacitinib	3.2–8 hours (Xeljanz XR package insert, 2021)	EDC – 2 days
Upadacitinib	8–14 hours (Rinvoq package insert, 2023)	EDC – 3 days
Mirikizumab	9.3 days (Omvoh package insert, 2023)	EDC – 47 days
Ustekinumab	19 days (Stelara package insert, 2019)	EDC – 95 days
Vedolizumab	25 days (Entyvio package insert, 2014)	EDC – 125 days
Ozanimod	11 days (Zeposia package insert, 2023)	EDC – 55 days

Table 3. Exposure windows of each advanced UC comparator medication

Comparator treatment	Elimination half-life[a]	Start of exposure window

Abbreviations: EDC, estimated date of conception; UC, ulcerative colitis
a When half-life is reported as a range (e.g., 8–9.5 days) the maximum reported half-life is used

9.3.2. Outcomes

The primary outcome of this study is MCM. The secondary outcomes are spontaneous abortion, pregnancy termination, gestational hypertension, pre-eclampsia, eclampsia, stillbirth, preterm birth, and SGA. All study outcomes will be identified on claims by ICD-10-CM diagnosis and procedure codes, CPT® procedure codes, and HCPCS procedure codes. All outcomes will be identified by claims-based algorithms, and potential cases of MCMs identified by these algorithms will be confirmed via medical record review to the extent possible for inclusion in the primary analysis. MCMs are the only outcome that will be adjudicated using medical records.

Table 4 describes the study algorithms that will be used. The algorithms with available PPVs have been validated in either the Optum Research Database (ORD) or the Healthcare Integrated Research Database (HIRD). Because the study populations drawn from both the ORD and the HIRD are similar, namely pregnant individuals who have commercial insurance in the US, these validation results are assumed to be similar across databases (i.e., accuracy measures in the ORD are expected to be similar in the HIRD and vice versa).

Lists of diagnostic and procedure codes used to identify outcomes are provided in ANNEX 3.

9.3.2.1. MCM (Primary Outcome)

MCMs and groups of MCMs will be defined according to the Metropolitan Atlanta Congenital Defects Program (MACDP) classification (MACDP, 2023; Correa-Villaseñor et al., 2003, Scheuerle & Tilson, 2002). Because exposures may cause only specific types of MCMs, and not others, an analysis of MCMs overall may be diluted such that true effects are missed (Palmsten et al., 2014, He et al., 2020). Thus, MCMs will be further stratified by organ system for descriptive analyses of the primary objective. If the overall sample size required for a comparative analysis of MCMs is achieved, exploratory comparative analyses stratified by MCM subtype of organ system will be conducted. It is also likely, however, that analyses of MCM subtypes will be underpowered, and, as such, the results will be interpreted with caution.

Given that there is no high-performing claims-based algorithm that can identify MCMs (Chomistek et al., 2023), the final report will utilize a two-step process to identify cases of MCMs. First, a highly sensitive claims-based algorithm (Algorithm A; see Table 4) will be used to identify all potential cases of MCM; this algorithm is highly sensitive due to its requirement of a single code from a broad list of MCM codes, which results in a high proportion of false positives (PPV: 44%; Chomistek et al., 2023). Second, medical record review of all potential cases of MCM will be sought to rule out false positives and identify true cases of MCM. The definition of MCM will exclude minor, genetic, prematurity-related,

and position-related (e.g., plagiocephaly) defects. Note that potential cases will be classified as cases or non-cases in the primary analysis only if a medical record with sufficient clinical detail can be located and procured; those with insufficient clinical detail with which to determine case status will be classified as having insufficient information and will be excluded from the analysis. If a medical record is procured, sufficient clinical detail will be determined in conjunction with clinical experts and defined in the adjudication manual provided to the clinical reviewers conducting medical record adjudication. Given the necessary process of acquiring medical records from eligible patients and having sufficient clinical detail to evaluate case status, confirmed cases are expected to comprise approximately 30% of all true MCMs in this study population (Section 9.4.3).

The interim and final reports will apply the highly sensitive Algorithm A, as well as a more specific algorithm (Algorithm B, detailed in Table 4) that requires more than one code for MCM and uses more specific codes that exclude minor malformations. Algorithm B is expected to have fewer false positives than Algorithm A (in the absence of validation) but could be less sensitive. MCMs identified by Algorithm B will identify a subset of those cases identified by Algorithm A. Each algorithm will be compared with medical records, and algorithm-specific PPVs will be reported for each study cohort. Both reports (interim and final) will include both algorithms for comparability across reports, but the main results included in the final report will be restricted to the subset of MCM cases identified by Algorithm A that are confirmed via medical records.

The main analysis will evaluate confirmed MCMs among linked liveborn infants, using codes from the pregnant individual's claims, infant's claims, and medical records when available. As noted in Section 9.2.8, infant outcomes will be ascertained through 12 months of age. Previous work in Optum Dynamic Assessment of Pregnancies and Infants (DAPI) observed that most congenital malformations were diagnosed within one month of birth, although the timing varied by type of malformation (Hughes et al., 2021). Hence, ascertainment through 12 months of age is expected to capture most MCMs. Length of follow-up among linked infants in this time period will be described.

9.3.2.1.1. Medical Record Validation of MCM

Medical records will be sought by Optum and Carelon Research, separately, for each potential case of MCM, to the extent possible. These requests will follow appropriate approvals and will be within the subset of individuals among whom patient-identifiable information may be accessed. Medical records can be requested for approximately 45-50% of study participants who are members of specific health insurance plans that allow the use of personal identifying information for research following appropriate approvals. Each potential case for whom a medical record is requested and received will be adjudicated following common data collection and adjudication rules. To limit the potential challenges in obtaining older medical records, medical record procurement will be conducted twice during the study, once following delivery of the interim report and once at the completion of the study for the final study report. Medical record adjudication will occur only once, at the end of the study.

Medical record confirmation will begin with a detailed review of the chronological listing of relevant claims (i.e., claims profile) for each of the potential cases in order to:

- Determine whether the claims listing for each potential case contains sufficient information (e.g., treating provider) to be included in the medical record procurement process; and
- Determine the medical site of treatment most likely to yield medical records with the necessary information to confirm case status.

For each potential case, one medical record will be requested from the primary provider. If a medical record cannot be obtained from this provider, a record will be requested from an alternate provider(s), if available. Of those that are requested, approximately 65-85% of medical records are expected to be successfully obtained in the ORD (Seeger et al., 2006; Johannes et al., 2007), along with approximately 65-70% of medical records in the HIRD.

Optum, in consultation with clinicians, will develop a standardized medical record review form that will include clinical elements necessary to confirm the outcome diagnosis, which will be used by Optum and Carelon Research. Providers will be asked to send all available medical information occurring during the period of interest (surrounding the service date of the relevant claim).

Optum and Carelon Research will, separately, identify two clinical consultants with expertise in the field of teratology for the adjudication of MCMs observed within their respective data sources. The pair of clinicians, who will both be blinded to exposure status, will review the clinical data for each potential case and adjudicate the outcomes; consensus will be sought for any discrepancies in adjudication results. Optum and Carelon Research will work with outside vendors as needed to procure the medical records and conduct the outcome adjudication according to standardized procedures and case definitions.

9.3.2.2. Spontaneous Abortion

Spontaneous abortion will be defined as pregnancy loss at < 20 completed weeks of gestation. Ectopic and molar pregnancies are excluded from the definition of spontaneous abortion. The outcome of spontaneous abortion will be identified on the claims of pregnant individuals based on diagnosis and/or procedure codes. The primary analysis will require the outcome to be identified at < 20 completed weeks of estimated gestational age; a sensitivity analysis will allow the outcome to be identified at < 22 completed weeks of gestation to address potential misclassification of gestational age.

9.3.2.3. Pregnancy Termination

Pregnancy termination will be defined as an intervention intended to terminate a pregnancy with medication or a medical procedure. Pregnancy termination will be identified on the claims of pregnant individuals based on diagnosis and/or procedure codes from EDC through 30 days after pregnancy end date.

9.3.2.4. Gestational Hypertension

Gestational hypertension will be defined as a systolic blood pressure of 140 millimeters of mercury (mm Hg) or more or a diastolic blood pressure of 90 mm Hg or more, or both, on two occasions at least 4 hours apart after 20 weeks of gestation in a pregnant patient with previously normal blood pressure (assessed by diagnosis code) (ACOG, 2020). Gestational hypertension will be identified on the claims of pregnant individuals based on ICD-10-CM

diagnosis codes. The primary analysis will require the outcome to be identified at ≥ 20 completed weeks of gestation; a sensitivity analysis will allow the outcome to be identified at ≥ 18 completed weeks of gestation. Another sensitivity analysis will restrict the denominator to pregnancies ≥ 20 completed weeks of gestation with observed outcomes.

9.3.2.5. Pre-eclampsia

Pre-eclampsia will be defined as 1) proteinuria with either a) systolic blood pressure of ≥ 140 mm Hg or diastolic blood pressure of ≥ 90 mm Hg on two occasions at least four hours apart after 20 weeks' gestation in an individual with previously normal blood pressure or b) systolic blood pressure of ≥ 160 mm Hg or diastolic blood pressure of ≥ 110 mm Hg; or, in the absence of proteinuria, 2) new-onset hypertension with the new onset of any of the following: thrombocytopenia, renal insufficiency, impaired liver function, pulmonary edema, or new-onset headache unresponsive to medication and not accounted for by alternative diagnoses or visual symptoms (ACOG, 2020). Pre-eclampsia will be identified on the claims of pregnant individuals based on ICD-10-CM diagnosis codes. The primary analysis will require the outcome to be identified at ≥ 20 completed weeks of gestation; a sensitivity analysis will allow the outcome to be identified at ≥ 18 completed weeks of gestation. Another sensitivity analysis will restrict the denominator to pregnancies ≥ 20 completed weeks of gestation with observed outcomes.

9.3.2.6. Eclampsia

Eclampsia will be defined as new-onset hypertensive tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use (ACOG, 2020). Eclampsia will be identified based on the claims of pregnant individuals based on ICD-10-CM diagnosis codes. The primary analysis will require the outcome to be identified at ≥ 20 completed weeks of gestation; a sensitivity analysis will allow the outcome to be identified at ≥ 18 completed weeks of gestation. Another sensitivity analysis will restrict the denominator to pregnancies ≥ 20 completed weeks of gestation with observed outcomes.

9.3.2.7. Stillbirth

Stillbirth will be defined as fetal death at ≥ 20 completed weeks of gestation. This outcome will be identified on the claims of pregnant individuals based on ICD-10-CM diagnosis codes. The primary analysis will require the outcome to be identified at ≥ 20 completed weeks of gestation; a sensitivity analysis will allow the outcome to be identified at ≥ 18 completed weeks of gestation. Another sensitivity analysis will restrict the denominator to pregnancies ≥ 20 completed weeks of gestation with observed outcomes.

9.3.2.8. SGA

SGA will be defined as a liveborn infant with birth weight < 10th percentile for gestational age at birth. This outcome will be identified on claims of either pregnant individuals and/or their infants based on ICD-10-CM diagnosis codes. The analysis will be restricted to singleton pregnancies and their liveborn linked infants.

9.3.2.9. Preterm Birth

Preterm birth will be defined as delivery of one or more liveborn infants at < 37 completed weeks of gestation. This outcome will be identified on claims of either pregnant individuals and/or their infants based on ICD-10-CM diagnosis codes. The primary analysis will be restricted to singleton pregnancies and their liveborn linked infants and will require the outcome to be identified at < 37 completed weeks of gestation. A sensitivity analysis will include all pregnancies with liveborn linked infants, and another will allow the outcome to be identified at < 39 completed weeks of gestation.

Table 4. Algorithms for the identification of pregnancy and infant outcomes in claims data

Outcome	Algorithm	Denominator for primary analysis	Outcome ascertainment window	Validity
Major congenital malformation	Highly sensitive algorithm (Algorithm A): ≥ 1 infant or pregnant individual dx code for MCM More specific algorithm (Algorithm B): ≥ 2 infant or pregnant individual dx codes for a smaller list of MCM codes at least 30 days apart	Pregnancies with a liveborn, linked infant	Up to 365 days after birth[a]	From Optum DAPI, highly sensitive MCM algorithm has PPV: 44% (95% CI: 35–53%); more specific MCM algorithm has PPV: 68% (95% CI: 56–80%) (Chomistek et al., 2023)
Spontaneous abortion	≥ 1 pregnant individual dx or px code for spontaneous abortion	All pregnancies with observed outcome(s)	Primary analysis: < 20 completed weeks of gestation Sensitivity analysis: < 22 completed weeks of gestation	From Optum DAPI, PPV: 85% (95% CI: 78–91%) (Chomistek et al., 2023)
Pregnancy termination	≥ 1 pregnant individual dx or px code for pregnancy termination	All pregnancies with observed outcome(s)	From EDC through 30 days after pregnancy end date	Not available

Table 4. Algorithms for the identification of pregnancy and infant outcomes in claims data

Outcome	Algorithm	Denominator for primary analysis	Outcome ascertainment window	Validity
Gestational hypertension	≥ 1 pregnant individual dx code for gestational hypertension	All pregnancies with observed outcome(s) Sensitivity analysis: Pregnancies ≥ 20 completed weeks of gestation with observed outcome(s)	Primary analysis: ≥ 20 completed weeks of gestation Sensitivity analysis: ≥ 18 completed weeks of gestation	Not available
Pre-eclampsia	≥ 1 pregnant individual dx code for pre-eclampsia	All pregnancies with observed outcome(s) Sensitivity analysis: Pregnancies ≥ 20 completed weeks of gestation with observed outcome(s)	Primary analysis: ≥ 20 completed weeks of gestation Sensitivity analysis: ≥ 18 completed weeks of gestation	From Optum DAPI, PPV: 86% (95% CI: 71–100%) based on ≥ 1 ICD-10-CM dx code from an inpatient stay (Chomistek et al., 2023)
Eclampsia	≥ 1 pregnant individual dx code for eclampsia	All pregnancies with observed outcome(s) Sensitivity analysis: Pregnancies ≥ 20 completed weeks of gestation with observed outcome(s)	Primary analysis: ≥ 20 completed weeks of gestation Sensitivity analysis: ≥ 18 completed weeks of gestation	Not available
Stillbirth	≥ 1 pregnant individual stillbirth dx or px code	All pregnancies with observed outcome(s)	Primary analysis: ≥ 20 completed weeks of gestation Sensitivity analysis: ≥ 18	From a US Sentinel System study including HIRD data, stillbirth PPV was 83% (95: CI: 71–91%) based on ICD-10-CM code indicating (1)

Table 4. Algorithms for the identification of pregnancy and infant outcomes in claims data

Outcome	Algorithm	Denominator for primary analysis	Outcome ascertainment window	Validity
		Sensitivity analysis: Pregnancies ≥ 20 completed weeks of gestation with observed outcome(s)	completed weeks of gestation	gestational age ≥ 20 weeks' gestation AND (2a) ≥ 1 stillbirth-related code with no codes for other recorded outcomes OR (2b) ≥ 2 stillbirth-related codes (Andrade et al., 2021)
Small for gestational age	≥ 1 infant or pregnant individual dx code for SGA	Singleton pregnancies with a liveborn, linked infant	Up to 30 days after delivery[b]	SGA PPV is 92% (95% CI: 82–97%) based on ≥ 1 ICD-9-CM code from delivery to delivery + 30 days (He et al., 2020) From Optum DAPI, SGA algorithm has PPV: 35% (95% CI: 15–54%) for ≥ 1 ICD-10-CM dx code (Chomistek et al., 2023)
Preterm birth	≥ 1 infant or pregnant individual dx code for preterm birth	Singleton pregnancies with a liveborn, linked infant	Primary analysis: < 37 completed weeks of gestation Sensitivity analysis: < 39 completed weeks of gestation	From Optum DAPI, preterm birth algorithm has PPV: 92% (95% CI: 82–100%) (Chomistek et al., 2023)

Table 4. Algorithms for the identification of pregnancy and infant outcomes in claims data

Outcome	Algorithm	Denominator for primary analysis	Outcome ascertainment window	Validity

Abbreviations: CI, confidence interval; DAPI, Dynamic Assessment of Pregnancies and Infants; dx, diagnosis; EDC, estimated date of conception; ICD-9-CM, International Classification of Diseases Ninth Revision, Clinical Modification; ICD-10-CM, International Classification of Diseases Tenth Revision, Clinical Modification; HIRD, Healthcare Integrated Research Database; MCM, major congenital malformation; PPV, positive predictive value; px, procedure; SGA, small for gestational age; US, United States
a Infants born near the end of the study period may not have a full 12 months in which to ascertain MCMs, in which case, their outcome ascertainment window will be truncated to reflect available follow-up time. For a list of full censoring criteria, see Section 9.2.8.
b For full censoring criteria, see Section 9.2.8.

9.3.3. Covariates

All members of the study cohorts will be described according to covariates derived from claims during the baseline period, unless otherwise specified. The baseline period is a minimum of six months and a maximum of two years prior to and including the EDC. Demographic attributes will be determined at the time of the EDC. Only baseline covariates will be used in propensity score modeling, with the exception of select characteristics that may be more likely to be captured during prenatal care and are unlikely to be affected by treatment (e.g., tobacco use).

A list of covariates is provided below, including demographics, risk factors for the study outcomes, and variables associated with treatment choice.

- Demographic attributes, including age at EDC, geographic area, and year of EDC
- Indicators of socioeconomic status, when available
- Healthcare utilization, including length of health plan enrollment and number of physician visits, emergency department visits, and hospitalizations
- ICD-10-CM codes indicative of prior or current participation in a clinical trial
- Reproductive history up to two years prior to EDC, including pregnancy history, history of infertility, history of major birth defects in previous pregnancies, and history of diagnoses associated with increased risk of adverse pregnancy outcomes
- Characteristics of prenatal care in the current pregnancy, including number and timing of prenatal care visits, number of ultrasounds performed, and utilization of amniocentesis, chorionic villous sampling, non-invasive prenatal testing (NIPT), and other fetal monitoring/diagnostic procedures, pregnancy and delivery-related procedures
- Pre-pregnancy body mass index (BMI) or obesity diagnosis
- Medication use and vaccination history during the current pregnancy
- Tobacco-, alcohol-, and substance use-related diagnoses during pregnancy

- Concurrent steroid or immunosuppressant medication use
- Prior and/or current use of teratogenic medications (ANNEX 2)
- Contraindications for etrasimod use
- Diagnoses associated with an increased severity of UC (e.g., number of UC diagnoses, pancolitis)
- Inflammatory diseases such as asthma, allergic rhinitis, atopic dermatitis, other atopic disease, and lupus erythematosus
- Autoimmune diseases such as thyroiditis and vitiligo
- Depression and anxiety
- Concurrent maternal medical conditions that may be risk factors for the study outcomes, including preexisting and gestational hypertension, preexisting and gestational diabetes, multiple gestation, kidney disease, liver disease (including but not limited to hepatitis), infection during pregnancy, hospitalization during pregnancy, cardiovascular disease, and pulmonary disease
- Indications for use of the comparator drugs, including but not limited to diagnoses for each of the following: rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, hidradenitis suppurativa, juvenile idiopathic arthritis, plaque psoriasis, psoriatic arthritis, uveitis, polyarticular course juvenile idiopathic arthritis, inflammatory bowel disease, and multiple sclerosis

In addition to these pre-specified covariates, the 25 most common medications, diagnosis codes, and procedure codes observed in the six-month baseline period will be evaluated in both study databases, separately by study cohort and exposure window. These lists will be examined to determine whether any additional covariates should be considered in the IPTW model and will help ensure that no important, measured confounders are missed (e.g., non-study medications used to treat symptoms of UC or other conditions related to UC).

9.4. Data Sources

The patients in this study will be drawn from the ORD and the HIRD.

9.4.1. The Optum Research Database (ORD)

The ORD contains eligibility, pharmacy, 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 more than 85 million individuals with both medical and pharmacy benefit coverage. For 2023, data are available for approximately 11 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 (e.g., physicians use the Centers for Medicare & Medicaid Services [CMS]-1500 format, and hospitals use the Universal Billing [UB]-04 format)
- ICD-10-CM diagnosis codes and procedure codes
- CPT® 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 the following:

- NDC
- Drug name
- Dosage form
- Drug strength
- Fill date
- Days' supply
- Cost information
- 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 reidentified following approval by an Institutional Review Board (IRB), and all data access conforms to applicable Health Insurance Portability and Accountability Act policies.

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

The ORD cohorts for this study will employ DAPI, a proprietary process that includes a set of capabilities and established algorithms that is applied to claims data to identify pregnancies, trimesters, and pregnancy outcomes, and to link the data of pregnant individuals and their infants in an ongoing manner, within the ORD (Bertoia et al., 2022). The algorithms are based on a combination of validated algorithms as reported in the literature and clinical input. Records of the pregnant individuals and their infants will be linked through the presence of a common unique family insurance identifier. 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 pairs of pregnant individuals and their infants are identified in this manner are accurate. In addition, claims(s) relating to the delivery must be within seven days of the infant's birthdate (or 32 days for multiples).

In comparison with the broader US population, the individuals of child-bearing age who are included in the ORD (and thus, DAPI) tend to be healthier, reflecting the underlying population of the commercial insurance enrollees, and they likely have an age distribution more skewed toward older age, reflecting the age distribution of individuals 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; of those, 85% 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. 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 pregnant individual. This may occur if the infant were to be added to the other parent's plan (rather than the birth parent's), if the parents were to switch from individual plans to a family health plan, or if the pregnant individual was covered under their parent's policy (in which case a separate plan would need to be purchased for the infant). While the reasons for switching of the infants' health plans may be related to coverage for treatments relating to infant outcomes, reasons for switching are likely non-differential with respect to exposure to UC treatments. Therefore, while estimates of prevalence may be underestimated due to the switching of health plans, estimates of relative prevalence should be unbiased.

For a subset of pregnant individuals and infants, Optum can (with appropriate approvals) access medical records for pregnant individuals or infants to confirm outcomes.

9.4.2. The Healthcare Integrated Research Database (HIRD)

The HIRD is a large administrative healthcare database maintained by Carelon Research for use in health outcomes and epidemiologic research. The HIRD is a longitudinal medical and pharmacy claims database from Elevance Health-affiliated health plan members across the US. Carelon Research is a subsidiary of Elevance Health.

Member enrollment, medical care (professional and facility claims), outpatient prescription drug dispensing, outpatient laboratory test result data, and healthcare utilization may be tracked for health plan members in the database dating back to January 2006. As of July 2024, the HIRD included over 91 million unique individuals with medical coverage and over 72 million unique individuals with medical and pharmacy claims information (Barron et al. 2025).

The HIRD includes pharmacy claims that can be used to identify dispensing and administration of medications; dispensing can be identified by NDC and GPI codes, and administration of medications can be identified by CPT® codes and HCPCS codes. These codes enable identification of the specific formulation, dose, and amount of each medication provided.

The HIRD also includes claims for each medical encounter, where providers list a primary diagnosis and secondary diagnoses. Relevant medical conditions are captured using the ICD-10-CM coding system. Medical procedures can also be identified in the HIRD using the

CPT, HCPCS, and ICD-10 Procedure Coding System (ICD-10-PCS) coding systems. Approximately 85% of claims in the HIRD are approved within 3 months.

Claims data in HIRD are updated monthly, with an approximate 3-month time lag for greater than 85% capture of paid medical claims. The lag time for pharmacy data is shorter, with approximately 98% paid within 30 days.

Subscriber information in the HIRD enables linkage to a variety of supplemental data sources, including the following: laboratory test results, electronic health records (EHR), oncology treatment information, vaccine registries, mortality data, social determinants of health data, race and ethnicity data, and others. With IRB approval, patients in the HIRD may be identified and then linked to providers, which enables the retrieval of medical records to supplement the healthcare claims data. For example, retrieval of patients' medical records may be used to perform outcome validation or to obtain supplementary information not available in the healthcare claims data.

9.4.2.1. Pregnancy and Infant Identification in the HIRD

Pregnancies will first be identified by the presence of an end of pregnancy (EOP) code during the study period. Because the HIRD pregnancy algorithm requires complete follow-up of pregnancies, it is assumed that patients who disenroll from the health plan have similar pregnancy outcome rates as those who do not disenroll. The LMP will be estimated by subtracting the estimated gestational age at the date of the EOP event from the date of the EOP event; the EDC will be defined as the LMP plus 14 days. Gestational age at the date of the EOP event will be estimated using available gestational age-related diagnosis and/or procedure codes from the records of pregnant individuals. The ICD-10-CM code for gestational weeks, Z3A, will be prioritized for use in gestational age estimation; this code is required for certain delivery claims by healthcare plans (e.g., cesarean delivery, preterm birth), and it is often reported during pregnancy (Jamal-Allial et al., 2019; Jamal-Allial et al., 2020).

When Z3A codes are unavailable, gestational age at the date of the EOP event will be estimated using a published internally validated pregnancy algorithm (Ailes et al. 2023).

Pregnant individuals will be linked to their liveborn infants within the HIRD using a combination of the subscriber identification number and alignment of the recorded delivery date and the infant's date of birth. This linkage provides a longitudinal record of diagnoses, procedures, and drug dispensings for the pregnant individual and infant.

9.4.3. Medical Records

As noted in Section 9.3.2.1.1, medical records will be sought by both Optum and Carelon Research for the adjudication of MCMs identified in their respective databases. MCM, the primary outcome, is the only outcome for which medical records will be sought. Medical records can be requested for approximately 45-50% of study participants who are members of specific health insurance plans that allow the use of personal identifying information for research following appropriate approvals. Among those requested, approximately 60-70% are received. Consequently, approximately 30-40% of potential cases of MCMs are

expected to have medical records available for adjudication across the Optum and Carelon data.

9.5. Study Size

Based on guidance from the FDA regarding the planning of pregnancy outcome studies, along with national vital statistics data in the US, approximately 3% of liveborn infants each year have an MCM (March of Dimes, 2015). It is estimated that 15.3% of recognized pregnancies result in spontaneous abortion (Quenby et al., 2021), 20.6% of pregnancies end in pregnancy termination (Jones et al., 2022), 6.5% of pregnancies are affected by gestational hypertension (Butwick et al., 2020), 3.8% of pregnancies are affected by pre-eclampsia (Ananth et al., 2013), 0.281% of pregnancies are affected by eclampsia (Butwick et al., 2020), and 0.5% of pregnancies end in stillbirth (FDA 2002). Approximately 10% of births are affected by SGA (Centers for Disease Control and Prevention, 2008), and approximately 8.71% result in preterm birth (Osterman et al., 2025).

Using these reference proportions and assuming complete case ascertainment as shown in Table 5, a minimal sample size of 214 etrasimod-exposed pregnancies with linked liveborn infants (with a matching ratio of 1:4) would provide 80% power to detect a prevalence ratio of 2.5 for the outcome of MCMs. The assumed prevalence for MCMs, however, does not account for the primary analysis being restricted to confirmed cases. Only 30-40% of patients in each database are expected to have medical records available for adjudication and confirmation of the MCM outcome (Section 9.4.3) (Seeger et al., 2006; Johannes et al., 2007). Therefore, the observed prevalence of confirmed MCMs may be reduced to 1-2%. Accordingly, 214 pregnancies linked to infants means the power of these primary analyses would be 40-48%. Given this limitation, secondary analyses that utilize all claims-based MCMs and have higher power will also be conducted and can contribute to the overall interpretation of findings.

If we were to assume complete case ascertainment of the primary outcome and assuming that 70% of pregnancies will result in a livebirth and 75% of infants will be linked with a 1:4 matching ratio, an estimated 408 etrasimod-exposed pregnancies would need to be accrued to yield 214 linked infants for evaluation. This sample size could be achieved with approximately 82 exposed pregnancies per year for five years across the two data sources. Under these same assumptions but with a lower matching ratio of 1:2, an estimated 510 etrasimod-exposed pregnancies would need to be accrued to yield 268 linked infants for evaluation.

Table 5. Estimated sample size[a] required for comparative analyses using matching ratios of 1:2, 1:3, and 1:4

Outcome	Prevalence of the outcome	Prevalence ratio	Etrasimod-exposed pregnancies[b] with observed outcomes needed, assuming a matching ratio of		
			1:2	1:3	1:4
Major congenital malformations	3%[c]	2 2.5 3 3.5	532 268 167 118	464 232 144 101	430 214 132 92
Spontaneous abortion	15.3%	2 2.5 3 3.5	86 42 25 17	75 37 22 15	70 34 21 14
Pregnancy termination	20.6%	2 2.5 3 3.5	58 28 16 11	51 24 14 10	47 23 13 9
Gestational hypertension	6.5%	2 2.5 3 3.5	233 116 72 50	203 101 62 43	189 93 58 40
Pre-eclampsia	3.8%	2 2.5 3 3.5	415 208 130 91	362 181 112 78	335 167 103 72
Eclampsia	0.281%	2 2.5 3 3.5	5,906 2,983 1,874 1,322	5,142 2,579 1,611 1,131	4,759 2,376 1,478 1,034
Stillbirth	0.5%	2 2.5 3 3.5	3,309 1,671 1,049 740	2,881 1,445 902 633	2,667 1,331 828 579
Small for gestational age	10%	2 2.5 3 3.5	143 71 44 30	125 62 38 26	116 57 35 24
Preterm birth	8.71%	2 2.5 3 3.5	168 84 52 36	147 73 45 31	136 67 41 29

Table 5. Estimated sample size[a] required for comparative analyses using matching ratios of 1:2, 1:3, and 1:4

Outcome	Prevalence of the outcome	Prevalence ratio	Etrasimod-exposed pregnancies[b] with observed outcomes needed, assuming a matching ratio of		
			1:2	1:3	1:4

a Sample size calculations were performed for a 2-sided α of 0.05 and a β of 0.8 under a likelihood ratio chi-square test for two independent proportions (SAS *proc power* procedure, *twosamplefreq* statement, *test=lrchi* option, and *groupweights* option specifying 1:2, 1:3 and 1:4 allocations).
b For major congenital malformations, small for gestational age, and preterm birth, counts represent the number of linked liveborn pregnancy-infant pairs needed.
c This is the presumed prevalence of the outcome among all linked liveborn infants, assuming complete case ascertainment for MCMs. Given that only 30-40% of patients are expected to have medical records available for adjudication and confirmation of the MCM outcome, the observed prevalence of MCMs may be reduced to 1-2%, which would reduce power for this outcome to 40-48% for a true prevalence ratio of 2.5 with 214 linked live-born infants in the etrasimod-exposed cohort, thereby generating wide confidence limits and uncertainty in comparative estimates

Table 6 presents counts of pregnant individuals with a diagnosis of UC from the ORD and the HIRD between 2018 and 2022. This represents the potential source population for this study, which will also include as a sensitivity analysis pregnant individuals who are exposed to etrasimod during pregnancy but who do not have a diagnosis of UC.

Table 6. Number of pregnant individuals with UC in the ORD and the HIRD, 2018-2022

Population	2018	2019	2020	2021	2022
Pregnant individuals with UC in the ORD	691	695	695	783	723
Pregnant individuals with UC in the HIRD	780	929	885	907	790

Abbreviations: UC, ulcerative colitis; ORD, Optum Research Database; HIRD, Healthcare Integrated Research Database

The actual study size will depend on uptake of etrasimod among patients included in the ORD and the HIRD. The interim report will assess accrual into the study cohorts and the feasibility of meeting the target study size. Additional data partners may be considered after the interim report if the number of etrasimod-exposed pregnancies remains below the target.

9.6. Data Management

All data analysis 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, as well as Instant Health Data (IHD) analytics software (Panalgo, Boston, MA, USA). The data will be extracted once per report. The interim report will include only claims-based data (i.e., no medical record information). The final report will include both claims-based data and the results of the medical record adjudication, as described in Section 9.3.2.1.1. All analyses will be performed in accordance with applicable laws and regulations. All reports and

deliverables will contain aggregated results only and will not identify individual patients, physicians, facilities, claims, or records data.

The following sections of the protocol (Sections 9.6.1 and 9.6.2) pertain to the data for the review of medical records described in Section 9.3.2.1.1.

9.6.1. Data Collection Tools

As used in this protocol, the term data collection tool (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 Carelon Research and should not be made available in any form to third parties, except for appropriate regulatory authorities, without written permission from Pfizer. Optum and Carelon Research 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 and Carelon Research have 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. To fulfill this responsibility, Optum and Carelon Research will confirm that a completed adjudication entry is provided by the reviewer for each medical record that is obtained and made available to the clinician reviewer(s) 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 should not obscure the original entry.

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 and Carelon Research agree to keep all study-related records, including sufficient information to link records (e.g., DCTs and hospital records), electronic copies of all DCTs, safety reporting forms, source documents, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, and telephone call reports). The records should be retained by Optum and Carelon Research according to local regulations or as specified in the Optum and Carelon Research contracts, whichever is longer. Optum and Carelon Research must ensure that the records continue to be stored securely for so long as they are retained.

If Optum or Carelon Research become unable for any reason to continue to retain study records for the required period (e.g., relocation), Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer.

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

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

9.7. Data Analysis

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

9.7.1. Interim Report

Interim analyses will be presented for pregnant individuals aged 15-50 years at EDC (which includes potential off-label users of etrasimod aged < 18 years, as well as women aged 18-50 consistent with age criteria per the etrasimod label). Additional analyses on pregnant individuals aged 15-50 years at EDC by age strata will be presented in the final report and are described in Section 9.7.4.

The interim report will include a description of the number and basic characteristics of pregnant individuals who have accrued into each of the cohorts by data source. Each study cohort will be described with respect to selected characteristics (e.g., age at EDC, year of EDC, select comorbidities). The group of individuals who are exposed to etrasimod during pregnancy but who do not have a diagnosis of UC will also be described. To gain insight into the use and potential switching of UC treatments by pregnant individuals, treatment patterns, including the number of patients who receive etrasimod alone, other advanced UC treatments alone, or both etrasimod and other advanced UC treatments will be summarized in table format for both the first trimester exposure window and the full pregnancy exposure window. A figure will be utilized to depict the switching or overlapping of treatments by individuals throughout pregnancy.

Counts of outcomes based on diagnosis and procedures codes, as well as the number of pregnancies eligible for each outcome, will be reported by data source. In addition, counts of censored infants will be reported, grouped by the reason for censoring (e.g., infant death, etc.). There will be no matching, weighting, comparative analysis or meta-analysis of data sources in the interim report. While an initial round of medical record procurement will be conducted for patients accrued into the study after the interim report in order to minimize the time from the occurrence of the outcomes until record procurement, the outcome of MCM will be based solely on claims data (i.e., obtained medical records will not be adjudicated until after delivery of the interim report).

9.7.2. Final Report

All descriptive and comparative analyses in the final report will be presented for pregnant individuals aged 15-50 years at EDC. In addition, the final report will present overall and age-stratified comparative analyses on pregnant individuals aged 15-50 years at EDC (potential off-label users of etrasimod) as described in Section 9.7.4.

9.7.2.1. Medical Record Validation Results

In the final report, the medical record validation results will be summarized separately by database. The number of MCMs identified in the claims-based algorithms, the subset eligible for medical record request, the subset with medical records retrieved, and the subset with confirmed MCMs will be reported. PPVs for Algorithms A and B will be calculated separately by cohort. Additionally, the sensitivity of Algorithm B relative to Algorithm A will be reported separately by cohort, based on the subset of MCMs identified by Algorithm A that also met Algorithm B criteria. Select characteristics of pregnancies that were eligible and ineligible for medical record review will be described.

9.7.2.2. Descriptive Analyses

The final report will include an attrition table detailing accrual of patients into each of the study cohorts, according to the study eligibility criteria, separately by database. Included for each cohort and for each data source in the attrition table will be the number of pregnancies identified in the claims, the number of livebirths, the number of pregnancies with multiple gestations, and the number of linked infants. As in the interim report, a summary of use patterns of UC treatments by pregnant individuals will be included in the final report, as well as a figure depicting these use patterns.

The study cohorts will be described with respect to all study covariates (Section 9.3.3), separately by database. Descriptive counts of study outcomes will be reported for each cohort, including for the sensitivity analysis of etrasimod-exposed pregnancies without a diagnosis of UC. Counts of infants censored from the primary analysis will be reported, grouped by the reason for censoring (e.g., infant death, etc.). Select characteristics of pregnancies ending in live birth with and without a linked infant will be presented.

9.7.2.3. Comparative Analyses

The comparative analyses described in this section will be conducted only if sufficient sample size is achieved (Section 9.5). For the final report, propensity score modeling and matching will be conducted on all individuals aged 15-50 at EDC who meet eligibility criteria and are assigned to a study cohort, stratified by age subgroup (i.e., < 18 years, 18-34 years, and 35-50 years). This stratified matching will be done so as to preserve the balance of covariates in the age subgroup analyses (Section 9.7.2.4). Within these age subgroups, pregnancies in the Etrasimod Cohort will be matched 1:4 to pregnancies in the Other Advanced UC Treatments Cohort on age (± 2 years) at EDC and calendar year of EDC. Analyses will be conducted among the set of patients remaining after this high-level match. The unmatched, matched, and matched and inverse probability of treatment (IPT)-weighted study cohorts will be described with respect to all study covariates (Section 9.3.3), separately by database. Similar descriptions will be provided among the subset with pregnancy or infant outcomes of interest.

The prevalence and the corresponding 95% CI for each study outcome will be estimated separately for each study cohort and within each database, and the results will be meta-analyzed using fixed effects analysis. In the final report, the prevalence ratio and 95% CI of MCM will be restricted to cases that are confirmed through medical record review, expected to comprise approximately 30% of all MCMs in the study population. The denominator for each calculation is described in Table 4. Prevalence estimates and comparative analyses will be restricted to pregnancies with an observed end-of-pregnancy outcome in the claims

data. A sensitivity analysis assessing the potential for selection bias due to pregnancies with unknown outcomes (e.g., pregnancies with Z3A codes indicating an ongoing pregnancy but no observed outcome) is described in Section 9.7.4.

For all study outcomes, unweighted and IPT-weighted prevalence ratios and corresponding 95% CIs comparing the Etrasimod Cohort to the Other Advanced UC Treatments Cohort will be estimated using log-binomial regression models in each data source, and a meta-analysis will be performed. For MCM, the prevalence ratio will be estimated using only confirmed cases. A sensitivity analysis will be conducted in which the PPV and sensitivity estimates obtained from the analysis of adjudicated MCMs will be applied to the claims-based estimates of relative prevalence to adjust the comparative estimates.

If an individual contributes more than one pregnancy to the analysis, robust standard errors will be used to account for covariance induced between observations (Mansournia et al., 2021). Confounders identified during the study (e.g., among the most common medications, diagnosis codes, and procedure codes as described in Section 9.3.3) that are strongly associated with etrasimod use and the pregnancy or infant outcomes may also be included in the outcome regression models. The prevalence of use of UC treatments during baseline and other covariates of interest will be evaluated for use as stratification variables.

The additional analyses described in Section 9.7.4 will be conducted for the final report only, with the exception of the sensitivity analysis describing characteristics and outcomes among individuals who are exposed to etrasimod during pregnancy but who do not have a diagnosis of UC.

9.7.2.4. Inverse Probability of Treatment Weighting

In the final study report only, sample size permitting, comparative analyses will be performed incorporating IPTW to adjust for potential confounding. The IPTW weights will be appropriately defined such that the causal estimate is the average treatment effect in the treated (ATT) (Austin & Stuart, 2015). Briefly, to estimate the ATT, the weights are defined such that every etrasimod-exposed pregnancy receives a weight of one, while the comparator pregnancies receive weights that are a function of the propensity score. The propensity score is the probability of being in the etrasimod-exposed group versus the comparator group and can incorporate dozens of demographic and clinical factors. In this study, all propensity score model variables will be evaluated during the baseline period and will be determined without respect to outcome status. Propensity score models will be run for the first trimester, 20-week, 37-week, and full pregnancy exposure windows, for a total of four models in each data source. To the extent that the decision to prescribe or use etrasimod depends on the health characteristics of the patient at the time of the decision, the propensity score models the clinical decision-making process. Because the weights are a function of this composite score, the groups will have comparable marginal distributions of the baseline characteristics after weighting.

The decision to include variables in the propensity score model will be based on *a priori* knowledge (e.g., expected confounder or known risk factor) (Hernan et al., 2002). Variables known (or highly suspected) to be confounders will be included in the model. To ensure that potential confounders are not inadvertently omitted, the most common diagnoses given, procedures administered, and drugs dispensed among members of the Etrasimod Cohort will be empirically defined; these lists will be reviewed, and those covariates that are known

risk factors for adverse pregnancy or infant outcomes will be identified and considered for inclusion in the propensity score model. Only baseline covariates will be used in propensity score modeling, with the exception of select variables that may be more likely to be captured during prenatal care and are unlikely to be affected by treatment (e.g., tobacco use). Thus, the propensity scores will capture patient characteristics at the start of the pregnancy.

Because patterns of prescribing tend to change over time, particularly for newly marketed products with early adopters of the formulation (both physician and patient) tending to differ from late adopters, prediction equations need to account for these secular changes. As such, the propensity score models may incorporate calendar time to account for the changing nature of the patient pool and UC treatment guidelines over time. Additional details will be provided in the SAP.

9.7.3. Missing Data

All information regarding exposure, outcome, and covariates will be derived from codes identified in the administrative claims. For such variables derived from the presence or absence of codes, there will be no missing values. For example, patients without an NDC code for etrasimod are presumed not to have filled a prescription for etrasimod, and patients without a code for diabetes are presumed to be non-diabetic. This may result in under-ascertainment (poor sensitivity) of conditions and exposures that are poorly coded (e.g., smoking status, obesity) or unavailable in the claims data (e.g., use of over-the-counter medications).

9.7.4. Additional Analyses

All additional analyses will be performed separately in each data source as sample size permits, and a meta-analysis will be performed. The following additional sensitivity and quantitative bias analyses will only be conducted in the final report, with the exception of the sensitivity analysis describing characteristics and outcomes among individuals who are exposed to etrasimod during pregnancy but who do not have a diagnosis of UC.

1. The primary analysis as described in Section 9.3.2.1 will be repeated, using all MCMs identified via the claims based MCM algorithms, including Algorithms A and B. A quantitative bias analysis will then be performed in which the estimated PPVs and sensitivities obtained from the analysis of adjudicated MCMs will be applied to the claims-based estimates of relative prevalence to correct for potential outcome misclassification arising from the fact that not all pregnancies are eligible for medical record retrieval, not all requested medical records are obtained, and not all obtained medical records contain enough information for a clear determination of case status. This correction will be implemented in accordance with the methods described by Lash et al. (2009).
2. A sensitivity analysis will evaluate MCMs in fetuses/infants from all pregnancies, expanding upon the primary analysis, which restricts to linked live births. Included will be pregnancies ending in live births, as well as those ending in an outcome other than live birth (i.e., spontaneous abortions, pregnancy terminations, stillbirths). Subsequently, a quantitative bias analysis will be conducted to quantify the potential bias arising from MCMs that might not have been observed in the primary analysis because they did not result in livebirths and thus may not have been captured in claims data. This analysis will make assumptions about the occurrence of MCMs

among pregnancies not ending in live births, and the corresponding effect on the prevalence ratios.

3. A quantitative bias analysis will be conducted to assess the degree of unmeasured confounding required to explain the observed relative prevalence (i.e., 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 et al., 2006). A sensitivity analysis will be performed to describe characteristics and outcomes among individuals who are exposed to etrasimod during pregnancy but who do not have a diagnosis of UC.
4. A sensitivity analysis for the analysis of MCMs will define etrasimod exposure as two or more dispensings during the first trimester exposure window to address potential exposure misclassification among pregnant individuals who fill a prescription for etrasimod but do not take it during the first trimester exposure window.
5. A subgroup analysis will repeat the primary analysis (Section 9.3.2.1) stratifying by age of the pregnant individual as follows:
    - 15-34 vs. ≥ 35 years at EDC, to account for the fact that pregnancies of advanced age (≥ 35 years) are at higher risk of some of the study outcomes, such as spontaneous abortion (Frick et al., 2021).
    - 18-50 vs. < 18 years at EDC, to examine potential differences in risk among per-label vs. off-label users of etrasimod.
6. Multiple gestation pregnancies are commonly at higher risk of SGA and preterm birth. While the primary analysis for SGA and preterm birth outcomes restricts to singleton pregnancies with liveborn linked infants, sensitivity analyses for these outcomes will include all births, including multiple gestation births, with liveborn linked infants (ACOG, 2023).
7. For gestational hypertension, pre-eclampsia, eclampsia, and stillbirth, a sensitivity analysis will restrict the denominator to pregnancies ≥ 20 completed weeks of gestation with observed outcomes.
8. A sensitivity analysis will exclude from the comparator group patients receiving ozanimod to address the potential influence of drug class effects.
9. A sensitivity analysis will restrict to patients with established UC diagnoses by requiring that a UC diagnosis be observed during the baseline period.
10. A sensitivity analysis will exclude individuals with a diagnosis code for CD during the baseline period and/or during pregnancy.
11. Sensitivity analyses will redefine the outcomes of spontaneous abortion, gestational hypertension, pre-eclampsia, eclampsia, stillbirth, and preterm birth using alternate outcome ascertainment windows to account for uncertainty in gestational age caused by the estimation of LMP, which is used to define the EDC. The following alternate outcome ascertainment windows will be used: < 22 completed weeks of gestation for spontaneous abortion; ≥ 18 completed weeks of gestation for gestational

hypertension, pre-eclampsia, eclampsia, and stillbirth; and < 39 weeks of gestation for preterm birth.

12. An analysis will be conducted to assess the potential impact due to the omission of pregnancies that have either no observed end-of-pregnancy outcome or, among completed pregnancies, no linked infant record. Characteristics of pregnancies with and without observed end-of-pregnancy outcomes will be described in the ORD only, as the HIRD does not identify pregnancies without end-of-pregnancy outcomes. Livebirth pregnancies with and without a linked infant will be described in both the ORD and the HIRD according to baseline covariates. If standardized mean differences > 0.1 are observed among variables pre-specified for inclusion in the propensity score model, a sensitivity analysis will be performed in which comparative analyses are weighted to adjust for censoring due to non-linkage.

9.8. Quality Control

9.8.1. Optum (ORD)

The ORD contains data derived from claims submitted by providers and pharmacies to obtain payment for health care services rendered, data to track plan membership for premium billing, and provider data to track participating physicians who have contracts with health plans to provide services. The underlying administrative data are routinely captured, verified, automated, and de-identified. The data undergo regular audits and quality control procedures by the insurer and are updated monthly. Although the health insurance claims data represent financial transactions and are not research records, the financial transactions related to the services provided create financial incentives to record them correctly and fully, so the billable medical services represented in the database are likely to be complete.

The 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), 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.

9.8.2. Carelon Research (HIRD)

The study will be tracked at various levels to help address project delivery, infrastructure, quality processes, resource management, and financial issues. To help ensure the highest level of quality on every project, Carelon Research has established several layers of quality assurance throughout the project lifecycle.

- Role-Based Control Checks: Each team member is responsible for performing thorough quality control checks on their work; in addition, the Principal Investigator and Research Project Manager are accountable for the quality of all deliverables.
- Quality Check Points: Centralized “checkpoints” have been implemented during the data management cycle to help ensure accurate translation of programming requests.
- Quality Assurance Standards: Standard review procedures have been developed and are applied throughout the project lifecycle.
- Automation: Carelon Research has developed standard definitions of many variables and disease states and developed programs to apply these standards as needed on projects. These standards help ensure consistency, repeatability, and accuracy for each project.

The Carelon Research team documents study progress and scientific and quality review of all study activities and deliverables (e.g., protocol, data management, data analysis, reports, manuscripts). This provides documentation of quality control measures performed for each study activity during the conduct of the study.

All programming required for study database extraction and creation of the analytic datasets from the HIRD will be performed per Carelon Research Programming Standards. The Carelon Research Programming Standards are documents describing data extraction methods referenced in Carelon Research SOPs and provide a guideline for basic, frequently used terms and definitions and respective coding information to maintain operational consistency. Data validation will occur throughout the data management and analysis process. Data quality checks include but are not limited to programming checks by an individual who is not the main programmer for the study, internal dataset consistency, and checks to ensure those protocol criteria are met.

9.9. Limitations of the Research Methods

This study is based on an analysis of automated and collected medical and prescription claims, supplemented by information abstracted from medical records. Data from claims databases are extremely valuable for the efficient and effective examination of health-related outcomes and effects of different exposures to treatment on those outcomes, and all claims databases have certain inherent limitations because the claims are collected for the purpose of payment as opposed to 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. 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. The presence of a diagnosis code on a medical claim is not positive presence of disease, as the diagnosis code may be incorrectly coded or included as rule-out criteria rather than actual disease. Additionally, relying on diagnosis codes to identify outcomes may include some individuals who do not meet the clinical definition of the outcome. Thus, there is the possibility of misclassification of exposures, outcomes, and covariates, which could result in bias.

Medical records will be reviewed for the primary study outcome of MCM when available to confirm cases that are initially identified via a highly sensitive claims-based algorithm, and the primary analysis will use an outcome definition that is restricted to include only confirmed cases. However, medical records are expected to be available for approximately 30% of patients in each database. Therefore, restricting the primary analysis to include only confirmed outcomes will result in an underestimation of MCMs. If this underestimation is non-differential with respect to exposure (i.e., 60% of true outcomes are confirmed in each exposure cohort), then the estimates comparing prevalence between the exposure cohorts would still be internally valid. Conversely, if this underestimation is differential with respect to exposure, then the estimates of relative prevalence would be biased; due to this possibility, we have proposed additional analyses to account for differential misclassification in the outcome (Section 9.7.4). Descriptive analyses comparing individuals who are eligible and ineligible for medical record request are planned to assess potential bias resulting from the restriction to individuals who are eligible. Sensitivity analyses will also be performed to utilize the claims-based MCM definitions and adjust for PPVs and estimated sensitivities obtained from adjudicated cases separately by cohort via quantitative bias analysis.

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 will miss MCMs that result in a spontaneous abortion, a pregnancy termination, a stillbirth, or MCMs among non-linked infants. For this reason, the estimates of prevalence of MCMs at birth may underestimate the true risk of MCMs among all pregnancies if the presence of an MCM is correlated with a higher risk of non-livebirth outcomes. If this underestimation is differential with respect to exposure cohort (i.e., the proportion of pregnancies with MCMs that result in non-livebirth outcomes is higher in one cohort), then this underestimation would result in biased

comparative estimates. Sensitivity analyses will be conducted to quantify and describe the impact this consideration may have on the observed relative prevalence. Descriptive analyses comparing pregnancies with and without a linked infant will help assess potential bias introduced by restricting to linked infants, and a sensitivity analysis will be performed if differences are observed. Additionally, the exploratory analyses of MCMs stratified by organ type are likely to be underpowered, but these analyses may still provide useful insight into the MCMs of greatest interest for future study if an increase in MCMs overall is observed.

MCMs will be identified in liveborn infants, and study drug exposure for this outcome will be assessed in the first trimester. However, the exact timing of the development of malformations is typically unknown (i.e., without weekly, accurate imaging of all fetuses). While MCMs typically originate in the first trimester, whether the malformation began to develop before drug exposure will be unknown for some pregnancies. For example, this could occur if the malformation began to develop at gestational week 8 and study drug exposure began at gestational week 10.

Some cases of spontaneous abortion and pregnancy termination may not be captured in the databases if the pregnant individual did not seek formal medical care or obtained medical care without using their insurance. Additionally, while the use of ICD-10-CM Z3A codes to estimate LMP was similar to estimated LMP from the medical record in a small validation study (Chomistek et al., 2023), not all pregnancies have Z3A codes, and some degree of measurement error is expected in estimating the beginning of pregnancy, especially in the absence of Z3A codes. The resulting exposure misclassification of EDC due to the estimation of LMP is expected to be non-differential with respect to exposure, as the same LMP estimation algorithm will be applied to all pregnancies (exposed and unexposed). Outcome-specific sensitivity analyses will be conducted to allow the identification of outcomes with less strict gestational age requirements.

The primary analysis will estimate the prevalence of gestational hypertension, pre-eclampsia, eclampsia and stillbirth among all pregnancies, as commonly reported in studies of adverse pregnancy outcomes. However, to be diagnosed with one of these outcomes, a pregnancy must survive to 20 weeks. Thus, an increased prevalence of early pregnancy loss or termination could result in an apparent decreased prevalence of these later adverse pregnancy outcomes due to depletion of susceptibles. To evaluate these outcomes accounting for the prevalence of early pregnancy loss, a sensitivity analysis will re-estimate the prevalence of gestational hypertension, pre-eclampsia, eclampsia and stillbirth among only pregnancies at risk of these outcomes at 20 weeks.

It is also possible that pregnancies terminating prematurely (e.g., due to spontaneous abortion) may have ended in another outcome (e.g., stillbirth) had they continued beyond 20 weeks. In this scenario, spontaneous abortion lies on the same causal pathway as stillbirth. To the extent that these outcomes share causal pathways, any observed differences among the study cohorts in the prevalences of stillbirth, gestational hypertension, pre-eclampsia and eclampsia should be interpreted in light of observed differences in the prevalences of spontaneous abortion and termination.

This study is focused on prevalence and does not consider time at risk; nor does it employ a sequential cohort design. However, for etrasimod and other study drugs taken for chronic conditions, we expect that for most pregnancies, exposure will begin very early in pregnancy. Within a sequential design framework, this is equivalent to a single sequential cohort, all of whom start exposure at the same time, at or near EDC. Assuming this is the case, the current design is expected to yield similar results to a sequential cohort study.

Residual confounding is always a concern in observational studies. In the present study, socioeconomic status may be a particular source of confounding, as it may affect both choice of UC treatment, as some treatments have higher patient costs than others, and pregnancy and infant outcomes. While propensity score models can account for many 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 study power will be limited until several years of cohort accrual have passed. Accrual of etrasimod-exposed pregnancies depends on actual use within the insured population that comprises the study source; therefore, divergence in numbers of users from sample size projections might affect how rapidly the study power reaches an adequate level.

9.10. Other Aspects

Not applicable

10. PROTECTION OF HUMAN PARTICIPANTS

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.

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

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, 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. There is no planned transfer of study data under this study protocol. At no time will Pfizer receive patient-identifying information.

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)/ Ethics Committee (EC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (e.g., informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC 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 following guidance documents:

- Guidelines for Good Pharmacoepidemiologic Practices issued by ISPE;
- European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology;
- FDA Guidance for Industry: Good Pharmacovigilance Practices and Pharmacoepidemiologic Assessment; and
- FDA Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study does not involve medical record review by the treating physician. External clinical adjudicators will review medical records to confirm select outcomes among a subset of patients, as described in Section 9.3.2.1.1.

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 (i.e., identify a potential association between) a particular product and a medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, or an 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 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 DCT and reported, within one business day of awareness of the study team 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, within one business day of awareness of the study team 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 etrasimod during pregnancy are not reportable unless associated with serious or non-serious AEs.
- 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, as 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 one patient identifier (e.g., gender, age as captured in the narrative field of the form) will be reported on the NIS AEM Report Form, thus allowing the report to be considered valid in accordance with pharmacovigilance legislation. All identifiers will be limited to generalities, such as the statement "a 35-year-old female…" or "an elderly male…"; other identifiers will have been removed.

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

All Optum and Carelon 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 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 YRR training materials. Where Pfizer issues an updated safety training program, including during the course of a calendar year, Optum and Carelon Research shall ensure that all research study staff members complete the updated safety training within sixty (60) calendar days of notification by Pfizer that an updated training has been issued.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report will be submitted to the US FDA. The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if Optum/Carelon Research 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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ANNEX 1. LIST OF STANDALONE DOCUMENTS

None.

ANNEX 2. LIST OF KNOWN TERATOGENIC MEDICATIONS

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
Androgen	Methyltestosterone	6 to 8 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
	Testosterone	10 to 100 min	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Testosterone cypionate	8 d	44 days prior to EDC	1st, 2nd, and 3rd trimesters
	Testosterone enanthate	4.5 d	25 days prior to EDC	1st, 2nd, and 3rd trimesters
	Mesterolone	12 to 13 h	3 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Nandrolone	144 to 288 h	66 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Oxandrolone	13.3 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Prasterone	12 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Fluoxymesterone	9.2 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Angiotensin II receptor antagonist	Azilsartan	11 h	3 days prior to EDC	1st trimester, 2nd, and 3rd trimesters
	Candesartan	9 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Eprosartan	20 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Irbesartan	11 to 15 h	4 days prior to EDC	1st, 2nd, and 3rd trimesters
	Losartan	2 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Olmesartan	13 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Tasosartan	Not available, but half-life of ARBs range from 1 to 3 d	17 days prior to EDC	1st, 2nd, and 3rd trimesters
	Telmisartan	24 h	6 days prior to EDC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Valsartan	6 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
Angiotensin-converting enzyme inhibitor	Benazepril	10 to 11 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Captopril	2 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Cilazapril	9 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Enalapril	11 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Fosinopril	11.5 to 14 h	4 days prior to EDC	1st, 2nd, and 3rd trimesters
	Lisinopril	12 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Moexipril	12 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Perindopril	0.8 to 1 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Quinapril	3 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Ramipril	13 to 17 h	4 days prior to EDC	1st, 2nd, and 3rd trimesters
	Trandolapril	6 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
Antiarrhythmic	Amiodarone	61 d	11 months prior to EDC	1st, 2nd, and 3rd trimesters
Antibiotic	Kanamycin	2 to 3 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Streptomycin	2 to 4.7 h	2 days prior to EDC	1 day prior to EDC, and 1st, 2nd, and 3rd trimesters
	Sulfamethoxazole/ Trimethoprim	8 to 10 h	3 months prior to EDC	3 months prior to conception and 1st trimester for MCMs and 2nd trimester for preterm birth and LBW
	Telavancin	8 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Demeclocycline	10 to 17 h	4 days prior to EDC	2nd and 3rd trimesters
	Oxytetracycline	6 to 11 h	3 days prior to EDC	2nd and 3rd trimesters
	Tetracycline	6 to 11 h	3 days prior to EDC	2nd and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Chlortetracycline	5.6 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Doxycycline	18 to 22 h	5 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Methacycline	14 to 22 h	5 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Minocycline	11 to 24.31 h	6 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Tigecycline	27 to 43 h	10 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Anticoagulant	Acenocoumarol	8 to 11 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Dicumarol	1 to 2 d	11 days prior to EDC	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Phenprocoumon	4 to 6 d	33 days prior to EDC	1st, 2nd, and 3rd trimesters
	Warfarin	40 h	10 days prior to EDC	At least 2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
Anticonvulsant	Lamotrigine	Adult, 25.4 to 70.3 h (healthy volunteers); 12.6 to 58.8 h (epilepsy)	17 days prior to EDC	1st, 2nd, and 3rd trimesters
	Trimethadione/Paramethadione	Paramethadione: 12 to 24 h Trimethadione: 11 to 16 h	6 days prior to EDC	1st, 2nd, and 3rd trimesters
	Valproic acid / Valproate / Divalproex sodium	9 to 16 h	4 days prior to EDC	Primarily 1st trimester, but MCMs have been associated with 2nd and 3rd trimester exposures.
	Carbamazepine	12 to 65 h	15 days prior to EDC	1st, 2nd, and 3rd trimesters
	Ethotoin	3 to 9 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Phenytoin / Fosphenytoin	Phenytoin: 7 to 42 h Fosphenytoin: 15 min	10 days prior to EDC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Primidone	10 h	3 days prior to EDC	1st, 2nd, and 3rd trimesters
	Topiramate	21 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Ethosuximide	17 to 56 h	13 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Methsuximide	3 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Oxcarbazepine	Oxcarbazepine: immediate-release formulations, about 2 h; extended-release tablet, 7 to 11 h Active metabolite, 10–monohydroxy: 9 to 11 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Sultiame	24 h	6 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Vigabatrin	10.5 h	3 days prior to EDC	Unknown
	Phenobarbital	70 to 140 h	33 days prior to EDC	1st, 2nd, and 3rd trimesters
	Methylphenobarbital	34 h	8 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Antidepressant	Brexanolone	9 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Esketamine	12 h	3 days prior to EDC	3 days prior to conception, and 2nd, and 3rd trimesters
	Paroxetine	21 h	5 days prior to EDC	5 days prior to conception, and 1st trimester
Antifungal	Fluconazole	30 h	2 weeks prior to EDC	2 weeks prior to conception and 1st trimester
	Flucytosine	2.4 to 4.8 h	2 days prior to EDC	1st trimester
Antineoplastic	Aminopterin	12 to 24 h	6 days prior to EDC	1st, 2nd, and 3rd trimesters
	Asparaginase	5.7 d	3 months prior to EDC	3 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Axitinib	2.5 to 6.1 h	1 week prior to EDC	1 week prior to conception and 1st, 2nd, and 3rd trimesters
	Brentuximab vedotin	4 to 6 d	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Methotrexate	55 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Crizotinib	42 h	45 days prior to EDC	45 days prior to conception and 1st, 2nd, and 3rd trimesters
	Cytarabine	1 to 3 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd 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 prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Exemestane	24 h	1 month prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Mechlorethamine	15 min	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Mercaptopurine	10 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vinblastine	24.8 h	6 days prior to EDC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Cyclophosphamide	3 to 12 h	12 months prior to EDC	12 months prior to conception and 1st trimester
	Altretamine	4.7 to 10.2 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Amsacrine	8 to 9 h	3 months prior to EDC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Bevacizumab	480 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Bleomycin	2 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bortezomib	40 to 193 h	7 months prior to EDC	7 months prior to conception and 1st, 2nd, and 3rd trimesters
	Busulfan	2.3 to 3.4 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Capecitabine	0.75 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Carboplatin	2.6 to 5.9 h	2 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Carmustine	15 to 75 min	1 day prior to EDC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Cetuximab	63 to 230 h	2 months prior to EDC	2 months prior to conception and 1st, 2nd, and 3rd trimesters
	Chlorambucil	1.5 h	1 day prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Cisplatin	120 h	14 months prior to EDC	14 months prior to conception and 1st,

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
				2nd, and 3rd trimesters
	Cladribine	1 d	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Clofarabine	5.2 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Dacarbazine	5 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Dactinomycin	36 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Dasatinib	3 to 5 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Edcetaxel	11.1 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Doxorubicin	20 to 48 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Epirubicin	31.1 h ± 6 h to 35.3 h ± 9 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Erlotinib	36.2 h	2 weeks prior to EDC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Estramustine	10 to 20 h	5 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Etoposide	4 to 11 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Fludarabine	20 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Fluorouracil	8 to 20 min	3 months prior to EDC	3 months prior to conception and 1st, 2nd, and 3rd trimesters
	Gemcitabine	1.7 to 19.4 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Hydroxycarbamide (Hydroxyurea)	2 to 4.5 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Idarubicin	20 to 22 h	6.5 months prior to EDC	6.5 months prior to conception and 1st, 2nd, and 3rd trimesters
	Ifosfamide	15 h	4 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Imatinib	18 h	2 weeks prior to EDC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Irinotecan	6 to 12 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Lapatinib	24 h	1 week prior to EDC	1 week prior to conception and 1st, 2nd, and 3rd trimesters
	Lomustine	16 to 48 h	2 weeks prior to EDC	2 weeks prior to conception and 1st, 2nd, and 3rd trimesters
	Melphalan	10 to 75 min	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Mitomycin	46 min	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Mitoxantrone	23 to 215 h	50 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Nelarabine	Adults: prodrug: 30 min; ara-G: 3 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Oxaliplatin	392 h	9 months prior to EDC	9 months prior to conception and 1st, 2nd, and 3rd trimesters
	Paclitaxel	13 to 52 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Pemetrexed	3.5 h	1 day prior to EDC	Unknown
	Pembrolizumab	22d	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Pentostatin	5.7 h	2 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Bevacizumab	480 h	6 months prior to EDC	6 months prior to conception, and 1st, 2nd, and 3rd trimesters
	Azacytidine	4 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bendamustine	40 min	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Decitabine	30 to 35 min	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bortezomib	40 to 193 h	45 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Brequinar	8 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Cabazitaxel	95 h	22 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Cabozantinib	55 h	13 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Dabrafenib	8 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Eribulin	40 h	10 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Everolimus	30 h	7 days prior to EDC	7 days prior to conception, and 1st trimester, 2nd, and 3rd trimesters
	Floxuridine	16 min	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Gefitinib	48 h	11 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Ixabepilone	52 h	12 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Lenvatinib	28 h	7 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Trimetrexate glucuronate	7 to 15 h	4 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Procarbazine	(IV), approximately 10 min	1 day prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Raltitrexed	260 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Sorafenib	25 to 48 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Streptozocine	Systemic: 35 min unchanged drug; 40 h metabolites	1 month prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Sunitinib	40 to 60 h	1 month prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tegafur	6.7 to 11.3 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Temozolomide	1.8 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Teniposide	5 h	2 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Thioguanine	80 min	1 day prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Thiotepa	1.4 to 3.7 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Topotecan	2 to 3 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vincristine	85 h	6 months prior to EDC	6 months prior to conception and 1st, 2nd, and 3rd trimesters
	Vindesine	2.9 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Vinorelbine	27.7 to 43.6 h	10 days prior to EDC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Lenalidomide	3 h	4 weeks prior to EDC	4 weeks prior to conception and 1st, 2nd, and 3rd trimesters
Antithyroid	Propylthiouracil	1 to 2 h	1 day prior to EDC	1st and 2nd trimesters
	Methimazole (Carbimazole)	4.9 to 5.7 h	2 days prior to EDC	1st, 2nd, and 3rd trimesters
	I-131 (radioiodine)	192 h	12 months prior to EDC	6 to 12 months prior to conception and 1st, 2nd, and 3rd trimesters
Antiviral	Ribavirin	12 d	66 days prior to EDC	1st, 2nd, and 3rd trimesters
Benzodiazepine	Clorazepate	50 to 70 h	16 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Endothelin receptor antagonist	Ambrisentan	15 h	4 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Bosentan	5 to 8 h	2 days prior to EDC	2 days prior to conception and 1st trimester
	Macitentan	16 to 48 h	11 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Estrogen	Diethylstilbestrol	Diethylstilbestrol reaches peak concentration within 20–40 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	17 days prior to EDC	1st, 2nd, and 3rd trimesters
Immuno-modulatory agent	Mycophenolate mofetil	16 h	4 days prior to EDC	1st, 2nd, and 3rd trimesters
	Thalidomide	5 to 7 h	1 month prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Penicillamine	2 to 4 h	1 day prior to EDC	1st, 2nd, and 3rd trimesters
	Azathioprine	5 h	2 days prior to EDC	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Leflunomide	432 to 456 h	2 years prior to EDC	2 years prior to conception and 1st, 2nd, and 3rd trimesters
	Mycophenolic acid	8 to 16 h	4 days prior to EDC	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Pomalidomide	9.5 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Teriflunomide	19 days	105 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Mood stabilizer	Lithium	24 h	6 days prior to EDC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
Nonsteroidal anti-inflammatory drug	Aspirin	30 h	7 days prior to EDC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exp
	Ibuprofen	2.2 h	1 day prior to EDC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exp
	Indomethacin	4.5 h	1 day prior to EDC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exp
	Naproxen	17 h	4 days prior to EDC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exp
Prostaglandins analogue	Misoprostol	20 to 40 min	1 day prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
Retinoid	Alitretinoin	9 h	1 month prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters
	Tretinoin	0.5 to 2 h	1 day prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	High dose Vitamin A (>10,000 IU/day)	TERIS only notes "long half-life"; 75 days per google search	14 months prior to EDC	1st, 2nd, and 3rd trimesters; doses above 10,000 IU/day may be teratogenic
	Acitretin	acitretin: 33 to 96 h; cis-acitretin: 28 to 157 h	3years prior to EDC	3 years prior to stopping treatment and throughout pregnancy, especially 1st trimester
	Bexarotene	7 h	2 days prior to EDC	2 days prior to conception, and 1st trimester
	Etretinate	120 d to 3 y	3 years prior to EDC	3 years prior to conception and throughout pregnancy, especially 1st trimester
	Isotretinoin	10 to 12 h	1 month prior to EDC	1 month prior to conception and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Tazarotene	18 h	5 days prior to EDC	1st, 2nd, and 3rd trimesters
	Retinol	2 to 9 h	12 months prior to EDC	12 months prior to conception and 1st trimester
Steroid	Danazol	9.7 to 23.7 h	6 days prior to EDC	1st, 2nd, and 3rd trimesters
Tyrosine kinase inhibitor	Afatinib	37 h	9 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Aflibercept	120 to 144 h	33 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Axitinib	2.5 to 6.1 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bosutinib	22.5 to 33.5 h	8 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Ceritinib	41 h	10 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Ibrutinib	4 to 6 h	2 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Lestaurtinib	NA	NA	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Nilotinib	17 h	4 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Nintedanib	10 to 15 h	4 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Other	Methylene blue	24 h	6 days prior to EDC	6 days prior to conception, and 1st, 2nd, and 3rd trimesters
	Riociguat	12 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Sparsentan	9.6 h	3 days prior to EDC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

Abbreviations: ara-G, guanine nucleoside analogue; ARB, angiotensin receptor blocker; EDC, estimated date of conception; IV, intravenous; LBW, low birth weight; MCM, major congenital malformation; NA, not applicable; TERIS, Teratogen Information System.

Drug Class	Generic Name	Half-Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window

[1] A woman will be considered exposed during the 1st trimester if a dose is taken during this pre-conception exposure window. The exposure window was calculated based on either at least 5 half-lives of the product or based on information from the literature, whichever is longer.
Sources: Eltonsy 2016; TERIS 2024; DrugBank online available at https://go.drugbank.com; product labels, which are available at: https://www.accessdata.fda.gov/scripts/cder/daf/ and https://dailymed.nlm.nih.gov/dailymed/index.cfm; summary of product characteristics at https://www.ema.europa.eu/en/medicines and https://products.mhra.gov.uk/, product monographs at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.

ANNEX 3. PREGNANCY AND INFANT OUTCOME CODES

All codes are ICD-10-CM diagnosis codes unless otherwise specified. These lists will be reviewed annually to update any changes since protocol finalization.

Pregnancy Outcomes

Pregnancy outcome codes provided in this Annex will be combined with estimates of gestational age to define outcomes, as described in Section 9.3.2. The pregnancy outcome codes to be assessed are:

- Spontaneous abortion
  - O02.1 Missed abortion
  - O03.0 Genital tract and pelvic infection following incomplete spontaneous abortion
  - O03.1 Delayed or excessive hemorrhage following incomplete spontaneous abortion
  - O03.2 Embolism following incomplete spontaneous abortion
  - O03.30 Unspecified complication following incomplete spontaneous abortion
  - O03.31 Shock following incomplete spontaneous abortion
  - O03.32 Renal failure following incomplete spontaneous abortion
  - O03.33 Metabolic disorder following incomplete spontaneous abortion
  - O03.34 Damage to pelvic organs following incomplete spontaneous abortion
  - O03.35 Other venous complications following incomplete spontaneous abortion
  - O03.36 Cardiac arrest following incomplete spontaneous abortion
  - O03.37 Sepsis following incomplete spontaneous abortion
  - O03.38 Urinary tract infection following incomplete spontaneous abortion

- O03.39 Incomplete spontaneous abortion with other complications
- O03.4 Incomplete spontaneous abortion without complication
- O03.5 Genital tract and pelvic infection following complete or unspecified spontaneous abortion
- O03.6 Delayed or excessive hemorrhage following complete or unspecified spontaneous abortion
- O03.7 Embolism following complete or unspecified spontaneous abortion
- O03.80 Unspecified complication following complete or unspecified spontaneous abortion
- O03.81 Shock following complete or unspecified spontaneous abortion
- O03.82 Renal failure following complete or unspecified spontaneous abortion
- O03.83 Metabolic disorder following complete or unspecified spontaneous abortion
- O03.84 Damage to pelvic organs following complete or unspecified spontaneous abortion
- O03.85 Other venous complications following complete or unspecified spontaneous abortion
- O03.86 Cardiac arrest following complete or unspecified spontaneous abortion
- O03.87 Sepsis following complete or unspecified spontaneous abortion
- O03.88 Urinary tract infection following complete or unspecified spontaneous abortion
- O03.89 Complete or unspecified spontaneous abortion with other complications
- O03.9 Complete or unspecified spontaneous abortion without complication
- O31.1 Continuing pregnancy after spontaneous abortion of one fetus or more
- O31.2 Continuing pregnancy after intrauterine death of one fetus or more
- O36.4 Maternal care for intrauterine death
- CPT®[2] 59800 Treatment of spontaneous abortion, first trimester
- CPT 59801 Treatment of spontaneous abortion, first trimester

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  - CPT 59810 Treatment of spontaneous abortion, second trimester
  - CPT 59811 Treatment of spontaneous abortion, second trimester
  - CPT 59812 Treatment of incomplete abortion, any trimester, completed surgically
  - CPT 59820 Treatment of missed abortion, completed surgically; first trimester
  - CPT 59821 Treatment of missed abortion, completed surgically; second trimester
  - CPT 59830 Treatment of septic abortion, completed surgically

- Pregnancy termination
  - O04.-- Complications following (induced) termination of pregnancy
  - O07.-- Failed attempted termination of pregnancy
  - Z33.2 Encounter for elective termination of pregnancy
  - 10A00ZZ Abortion of Products of Conception, Open Approach
  - 10A03ZZ Abortion of Products of Conception, Percutaneous Approach
  - 10A04ZZ Abortion of Products of Conception, Percutaneous Endoscopic Approach
  - 10A07Z6 Abortion of Products of Conception, Vacuum, Via Natural or Artificial Opening
  - 10A07ZW Abortion of Products of Conception, Laminaria, Via Natural or Artificial Opening
  - 10A07ZX Abortion of Products of Conception, Abortifacient, Via Natural or Artificial Opening
  - 10A07ZZ Abortion of Products of Conception, Via Natural or Artificial Opening
  - 10A08ZZ Abortion of Products of Conception, Via Natural or Artificial Opening Endoscopic
  - HCPCS S0190 Mifepristone, oral, 200 mg
  - HCPCS S0191 Misoprostol, oral, 200 mcg
  - HCPCS S0199 Medically induced abortion by oral ingestion of medication including all associated services and supplies
  - HCPCS S2260 Induced abortion, 17 to 24 weeks
  - HCPCS S2262 Abortion for maternal indication, 25 weeks or greater

- HCPCS S2265 Induced abortion, 25 to 28 weeks
- HCPCS S2266 Induced abortion, 29 to 31 weeks
- HCPCS S2267 Induced abortion, 32 weeks or greater
- CPT 01965 Anesthesia for incomplete or missed abortion procedures
- CPT 01966 Anesthesia for induced abortion procedures
- CPT 59840 Induced abortion, by dilation and curettage
- CPT 59841 Induced abortion, by dilation and evacuation
- CPT 59850 Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines;
- CPT 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
- CPT 59852 Induced abortion, by 1 or more intra-amniotic injections (amniocentesis-injections), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed intra-amniotic injection)
- CPT 59855 Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g.,, laminaria), including hospital admission and visits, delivery of fetus and secundines
- CPT 59856 Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., laminaria), including hospital admission and visits, delivery of fetus and secundines; with dilation and curettage and/or evacuation
- CPT 59857 Induced abortion, by 1 or more vaginal suppositories (e.g., prostaglandin) with or without cervical dilation (e.g., laminaria), including hospital admission and visits, delivery of fetus and secundines; with hysterotomy (failed medical evacuation)

- Gestational hypertension
  - O13.- Gestational [pregnancy-induced] hypertension without significant proteinuria
- Pre-eclampsia
  - O14.-- Pre-eclampsia
  - O11.- Pre-existing hypertension with pre-eclampsia

- Eclampsia
  - O15.-- Eclampsia
- Stillbirth
  - O31.0---Papyraceous fetus
  - O31.2---Continuing pregnancy after intrauterine death of one fetus or more
  - O36.4---Maternal care for intrauterine death
  - P95 Stillbirth
  - Z37.1 Single stillbirth
  - Z37.3 Twins, one liveborn and one stillborn
  - Z37.4 Twins, both stillborn
  - Z37.60 to Z37.64, Z37.69 Multiple births, some liveborn
  - Z37.7 Other multiple births, all stillborn
- Livebirth
  - O60.1--- Preterm labor with preterm delivery
  - O60.2---Term delivery with preterm labor
  - Z37.0 Single livebirth
  - Z37.2 Twins, both liveborn
  - Z37.50 Multiple births, unspecified, all liveborn
  - Z37.51 Triplets, all liveborn
  - Z37.52 Quadruplets, all liveborn
  - Z37.53 Quintuplets, all liveborn
  - Z37.54 Sextuplets, all liveborn
  - Z37.59 Other multiple births, all liveborn
  - Z38.00 Single liveborn infant, delivered vaginally
  - Z38.01 Single liveborn infant, delivered by cesarean
  - Z38.1 Single liveborn infant, born outside hospital
  - Z38.2 Single liveborn infant, unspecified as to place of birth
  - Z38.30 Twin liveborn infant, delivered vaginally
  - Z38.31 Twin liveborn infant, delivered by cesarean
  - Z38.4 Twin liveborn infant, born outside hospital

- Z38.5 Twin liveborn infant, unspecified as to place of birth
- Z38.61 Triplet liveborn infant, delivered vaginally
- Z38.62 Triplet liveborn infant, delivered by cesarean
- Z38.63 Quadruplet liveborn infant, delivered vaginally
- Z38.64 Quadruplet liveborn infant, delivered by cesarean
- Z38.65 Quintuplet liveborn infant, delivered vaginally
- Z38.66 Quintuplet liveborn infant, delivered by cesarean
- Z38.68 Other multiple liveborn infant, delivered vaginally
- Z38.69 Other multiple liveborn infant, delivered by cesarean
- Z38.7 Other multiple liveborn infant, born outside hospital
- Z38.8 Other multiple liveborn infant, unspecified as to place of birth

The following livebirth codes are used to identify livebirths in multiple gestation pregnancies with more than one outcome type:

- Z37.3 Twins, one liveborn and one stillborn
- Z37.60 Multiple births, unspecified, some liveborn
- Z37.61 Triplets, some liveborn
- Z37.62 Quadruplets, some liveborn
- Z37.63 Quintuplets, some liveborn
- Z37.64 Sextuplets, some liveborn
- Z37.69 Other multiple births, some liveborn

Infant Outcomes

Infant outcome codes will be identified on the records of the pregnant individual or infant, as described in Section 9.3.2. The infant outcomes to be assessed are:

- Preterm birth
  - O60.1 Preterm labor with preterm delivery
  - P07.2 Extreme immaturity of newborn
  - P07.20 Extreme immaturity of newborn, unspecified weeks of gestation
  - P07.21 Extreme immaturity of newborn, gestational age less than 23 completed weeks
  - P07.22 Extreme immaturity of newborn, gestational age 23 completed weeks

- P07.23 Extreme immaturity of newborn, gestational age 24 completed weeks
- P07.24 Extreme immaturity of newborn, gestational age 25 completed weeks
- P07.25 Extreme immaturity of newborn, gestational age 26 completed weeks
- P07.26 Extreme immaturity of newborn, gestational age 27 completed weeks
- P07.3 Preterm [premature] newborn [other]
- P07.30 Preterm newborn, unspecified weeks of gestation
- P07.31 Preterm newborn, gestational age 28 completed weeks
- P07.32 Preterm newborn, gestational age 29 completed weeks
- P07.33 Preterm newborn, gestational age 30 completed weeks
- P07.34 Preterm newborn, gestational age 31 completed weeks
- P07.35 Preterm newborn, gestational age 32 completed weeks
- P07.36 Preterm newborn, gestational age 33 completed weeks
- P07.37 Preterm newborn, gestational age 34 completed weeks
- P07.38 Preterm newborn, gestational age 35 completed weeks
- P07.39 Preterm newborn, gestational age 36 completed weeks
- P59.0 Neonatal jaundice associated with preterm delivery

- Small for gestational age
  - P05.1--- Newborn small for gestational age
  - P05.0--- Newborn light for gestational age
- Major congenital malformations

The following list of congenital malformation subcategories and codes is based on the Metropolitan Atlanta Congenital Defects Program (MACDP, 2023) and may be further updated, adjusted or refined as appropriate.

Type of congenital malformation	**ICD-10-CM code**
All anomalies	Q-chapter, D21.5, D82.1, P35.0, P35.1, P37.1
Nervous system	Q00*, Q01*, Q02, Q03*, Q04*, Q05*, Q06*, Q07**
Neural tube defects	Q01*, Q05*
Anencephaly and similar malformations	Q00*

Type of congenital malformation	ICD-10-CM code
Encephalocele	Q01*
Spina bifida	Q05*
Hydrocephalus	Q03*
Microcephaly	Q02
Arhinencephaly/holoprosencephaly	Q04.1, Q04.2
Eye	Q10*, Q11*, Q12*, Q13**, Q14*, Q15*
Anophthalmos/microphthalmos	Q11.0, Q11.1, Q11.2
Congenital cataract	Q12.0
Congenital glaucoma	Q15.0
Ear, face, and neck	Q16*-Q18*
Anotia	Q16.0
Circulatory System	Q20*, Q21*, Q22*, Q23*, Q24*, Q25**, Q26*, Q27**, Q28*
Severe congenital heart defects	Q20.0, Q20.1, Q20.3, Q20.4, Q21.2, Q21.3, Q22.0, Q22.4, Q22.5, Q22.6, Q23.0, Q23.2, Q23.3, Q23.4, Q25.1, Q25.2*, Q26.2
Common arterial truncus	Q20.0
Double outlet right ventricle	Q20.1
Transposition of great vessels	Q20.3
Single ventricle	Q20.4
Ventricular septal defect (VSD)	Q21.0
Atrial septal defect (ASD)	Q21.1
Atrioventricular septal defect (AVSD)	Q21.2
Tetralogy of Fallot	Q21.3
Tricuspid atresia and stenosis	Q22.4
Ebstein's anomaly	Q22.5
Pulmonary valve stenosis	Q22.1
Pulmonary valve atresia	Q22.0
Aortic valve atresia/stenosis	Q23.0
Mitral valve anomalies	Q23.2, Q23.3
Hypoplastic left heart	Q23.4
Hypoplastic right heart	Q22.6
Coarctation of aorta	Q25.1
Aortic atresia / interrupted aortic arch	Q25.2*
Total anomalous pulmonary venous return (TAPVR)	Q26.2

Type of congenital malformation	ICD-10-CM code
Patent ductus arteriosus (PDA) as only congenital heart disease (CHD) in term infants (gestational age +37 weeks)	Q25.0
Respiratory	Q30*-Q34*
Choanal atresia	Q30.0
Cystic adenomatoid malformation of lung	Q33.0
Oro-facial clefts	Q35*-Q37*
Cleft lip with or without cleft palate	Q36*, Q37*
Cleft palate	Q35*
Digestive system	Q38*-Q45*, Q79.0
Esophageal atresia with or without trachea-esophageal fistula	Q39.0, Q39.1
Duodenal atresia or stenosis	Q41.0
Atresia or stenosis of other parts of small intestine	Q41.1, Q41.2, Q41.8
Ano-rectal atresia and stenosis	Q42.0-Q42.3
Hirschsprung's disease	Q43.1
Atresia of bile ducts	Q44.2
Annular pancreas	Q45.1
Diaphragmatic hernia	Q79.0
Abdominal wall defects	Q79.2, Q79.3, Q79.5*
Gastroschisis	Q79.3
Omphalocele	Q79.2
Urinary	Q60*, Q61**, Q62**, Q63*, Q64**, Q79.4
Bilateral renal agenesis including Potter syndrome	Q60.1, Q60.6
Multicystic renal dysplasia	Q61.4
Congenital hydronephrosis	Q62.0
Bladder exstrophy and/or epispadias	Q64.0, Q64.1*
Posterior urethral valve and/or prune belly	Q64.2, Q79.4
Genital	Q50**, Q51***, Q52***, Q54*, Q55**, Q56*
Hypospadias	Q54*
Indeterminate sex	Q56*
Musculoskeletal	Q65**, Q66***, Q67*, Q68*, Q69*, Q70**, Q71***, Q72***, Q73*, Q74*, Q75*, Q76***, Q77*, Q78*, Q79**
Limb reduction defects	Q71***, Q72***, Q73*
Club foot – talipes equinovarus	Q66.0*

Type of congenital malformation	ICD-10-CM code
Hip dislocation and/or dysplasia	Q65.0*, Q65.1, Q65.2, Q65.80, Q65.81
Polydactyly	Q69*
Syndactyly	Q70**
Other anomalies/syndromes	
Skeletal dysplasias	Q74.0, Q77*, Q78.0, Q78.2-Q78.8
Craniosynostosis	Q75.0
Congenital constriction bands/amniotic band	Q79.8
Situs inversus	Q89.3
Conjoined twins	Q89.4
Congenital skin disorders	Q80*-Q82*
VATER/VACTERL	Q87.2
Laterality anomalies	Q20.6, Q24.0, Q33.8, Q89.0*, Q89.3
Teratogenic syndromes with malformations	Q86*, P35.0, P35.1, P37.1
Fetal alcohol syndrome	Q86.0
Valproate syndrome	Q86.8
Maternal infections resulting in malformations	P35.0, P35.1, P37.1

* Indicates how many additional decimal places should be included in the wildcard, including the number listed. For instance, Q93
** should include the following: Q93 (non-billable), Q93.0, Q93.1, Q93.2, Q93.3, Q93.4, Q93.5 (non-billable), Q93.51, Q93.59, Q93.7, Q93.8 (non-billable), Q93.81, Q93.82, Q93.88, Q93.89, Q93.9.

Codes that were included in the MACDP ICD-9-CM code list but are no longer classified as congenital malformations in the new ICD-10-CM categorization will not be included in the MCM definition but are listed here for completeness.

- E78.71 Barth syndrome
- E78.72 Smith-Lemli-Opitz syndrome
- M21.021 Valgus deformity, not elsewhere classified, right elbow
- M21.022 Valgus deformity, not elsewhere classified, left elbow
- M21.029 Valgus deformity, not elsewhere classified, unspecified elbow
- M21.121 Varus deformity, not elsewhere classified, right elbow
- M21.122 Varus deformity, not elsewhere classified, left elbow
- M21.129 Varus deformity, not elsewhere classified, unspecified elbow
- P02.8 Newborn affected by other abnormalities of membranes
- P29.3 Persistent fetal circulation (typically a birth complication and not a defect)

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