Study information

Title	A Post-Marketing Safety Study to Evaluate the Safety of VELSIPITY® (Etrasimod) Exposure During Pregnancy
Protocol number	C5041043
Protocol version identifier	4.0
Date	23 January 2026
EU Post Authorization Study (PAS) register number	EUPAS1000000672
Active substance	Selective sphingosine 1-phosphate receptor ($S1P_{1,4,5}$) modulator
Medicinal product	VELSIPITY®
Research question and objectives	The research question is: Is there an increased risk of adverse maternal, fetal, or infant outcomes among individuals who are exposed to etrasimod during pregnancy? The primary objective of the study is to estimate the prevalence of major congenital malformations (MCMs) among pregnant individuals with moderate-to-severe ulcerative colitis (UC) who are exposed to etrasimod during pregnancy. The secondary objectives of the study are: • To estimate the prevalence of other maternal, fetal, and infant outcomes among pregnant individuals with moderate-to-severe UC who are exposed to etrasimod during pregnancy. • To contextualize the prevalence of outcomes among pregnant individuals who are exposed to etrasimod during pregnancy and to estimate the prevalence of all outcomes of interest among pregnant individuals with moderate-to-severe UC who are not exposed to etrasimod during pregnancy. • If sample size permits, to estimate the risk ratio (RR) for each study outcome comparing the outcomes of pregnant individuals with moderate-to-severe UC who are exposed to etrasimod with those who are not exposed to etrasimod.
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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACOG	American College of Obstetrics and Gynecology
ara-G	Guanine nucleoside analogue
ARB	Angiotensin receptor blocker
ART	Assisted reproductive technology
CDC	Centers for Disease Control and Prevention
CI	Confidence interval
DOC	Date of conception
EC	Ethics committee
EDD	Estimated date of delivery
FDA	Food and Drug Administration
HCP	Healthcare provider
HMA-EMA	Heads of Medicines Agencies-European Medicines Agency
IBD-PR	CorEvitas Inflammatory Bowel Disease Pregnancy Registry
INTERGROWTH-21st	International Fetal and Newborn Growth Consortium for the 21st Century
IPTW	Inverse probability of treatment weighting
IRB	Institutional review board
IV	Intravenous
LBW	Low birth weight
LMP	Last menstrual period
MACDP	Metropolitan Atlanta Congenital Defects Program
MCM	Major congenital malformation
N/A	Not applicable
PASS	Post-authorization safety study
RR	Risk ratio
RWD	Real-world data
S1P	Sphingosine 1-phosphate
SAB	Spontaneous abortion
SAP	Statistical analysis plan
SGA	Small for gestational age
TERIS	Teratogen Information System
UC	Ulcerative colitis
US	United States
VRCC	Virtual registry coordinating center
WHO	World Health Organization

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

Title: A Post-Marketing Safety Study to Evaluate the Safety of VELSIPITY™ (Etrasimod) Exposure During Pregnancy

Version and Date of Protocol: Version 4.0, 23 January 2026

Main authors: Shahar Shmuel, ScM, PhD, Pfizer, Inc, New York, USA; Ronna L. Chan, PhD, MPH, PPD Observational Studies of Thermo Fisher Scientific, North Carolina, USA

Rationale and background: Etrasimod is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis (UC). Etrasimod is a potent, orally bioavailable sphingosine 1-phosphate (S1P) receptor modulator that selectively activates S1P receptor subtypes 1, 4, and 5, with no detectable activity on $S1P_{2,3}$.
There are limited data on the safety of etrasimod use during pregnancy. Available data from reports of pregnancies from the etrasimod clinical development program are insufficient to identify a drug-associated risk of major birth defects, spontaneous abortion, or other adverse maternal or fetal outcomes; however, the S1P receptor plays an important role in embryogenesis, including vascular and neural development.
This non-interventional study is designated as a post-authorization safety study (PASS) and is a postmarketing requirement of the Food and Drug Administration.

Research question and objectives: The research question is: Is there an increased risk of adverse maternal, fetal, or infant outcomes among individuals who are exposed to etrasimod during pregnancy?
The primary objective of the study is to estimate the prevalence of major congenital malformations (MCMs) among pregnant individuals with moderate-to-severe UC who are exposed to etrasimod during pregnancy.
The secondary objectives of the study are:

- To estimate the prevalence of other maternal, fetal, and infant outcomes among pregnant individuals with moderate-to-severe UC who are exposed to etrasimod during pregnancy.
- To contextualize the prevalence of outcomes among pregnant individuals who are exposed to etrasimod during pregnancy and to estimate the prevalence of all outcomes of interest among pregnant individuals with moderate-to-severe UC who are not exposed to etrasimod during pregnancy.
- If sample size permits, to estimate the risk ratio (RR) for each study outcome comparing the outcomes of pregnant individuals with moderate-to-severe UC who are exposed to etrasimod with those who are not exposed to etrasimod.

Study design: This observational cohort study aims to estimate the prevalence of maternal, fetal, and infant outcomes among individuals with moderate-to-severe UC who are exposed to etrasimod during pregnancy.
Population: The study population will include two cohorts of pregnant individuals: one cohort of individuals with a diagnosis of moderate-to-severe UC who are exposed to etrasimod during pregnancy and one cohort of individuals with a diagnosis of moderate-to-severe UC who are not exposed to etrasimod during pregnancy.

Variables: Individuals will be considered exposed during pregnancy if at least one dose of a product is taken during pregnancy or up to at least 5 times the product's half-life prior to conception. Based on the half-life of etrasimod (approximately 30 hours), individuals will be considered exposed to etrasimod during pregnancy if a dose is taken within 7 days prior to conception. The primary outcome of interest is MCMs. The maternal and pregnancy secondary outcomes include minor congenital malformations, pre-eclampsia, eclampsia, spontaneous abortion, stillbirth, pregnancy termination, preterm birth, small for gestational age, gestational diabetes, gestational hypertension, and placental abruption. The infant secondary outcomes during the first year of life include postnatal growth deficiency, infant developmental delay, infant hospitalization, infant infections (both serious and non-serious), and infant death. Covariates will include demographics, risk factors for the study outcomes, comorbidities, concomitant medications, and predictors of treatment with etrasimod.

Data source: The study will use secondary data collected from the CorEvitas Inflammatory Bowel Disease Pregnancy Registry (IBD-PR), a prospective pregnancy registry based in the US and Canada.

Study size: The study aims to include a target sample size of 728 pregnant individuals (364 in each cohort). The minimum sample size to estimate the prevalence of the primary outcome, MCM, with meaningful confidence and precision, is 400 participants (200 in each cohort).

Data analysis: Participant characteristics will be summarized with descriptive statistics for each cohort. Comparative analyses will be conducted for each outcome if sample size permits. Additional analyses will be conducted that include pregnant individuals who were excluded from the analysis population. If sample size permits, subgroup, supplementary, and sensitivity analyses will be performed to examine the extent to which changes in certain methods or assumptions affect the results.

Milestones: The IBD-PR launched on 19 March 2025. For this PASS, yearly interim reports are planned: the first interim report will be provided to the FDA approximately one year after the first participant is enrolled in the IBD-PR; the end of data collection is planned for 30 September 2032; and the final study report is planned for 30 September 2033.

4. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (Substantial or Administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1.0	18 February 2025	Substantial	Abstract and Sections 9.1, 9.3.4 (Table 1), 9.5.3 (Tables 2 and 3), and 9.7.3 (Table 4)	Added maternal gestational diabetes, pregnancy-induced hypertension, and placental abruption outcomes, as well as infant hospitalization, infant infections (both serious and non-serious), and infant death outcomes as secondary outcomes.	Requested by the FDA
			Abstract as well as Section 9.1, 9.3.4 (Table 1), 9.3.5, 9.5.3 (Tables 2 and 3), and 9.7.3 (Table 4)	Replaced the term “elective” from the secondary outcome “elective termination” with “pregnancy termination.”	To align with the ACOG guidelines, as requested by the FDA
			Abstract and Section 6	Updated the number of interim reports (from 1 to annual), with the first interim report being provided to the FDA one year after the first participant is enrolled in the IBD-PR. Added “estimated date of first participant enrolled in IBD-PR” milestone and updated the start of data collection date and footnote 1 to clarify that the start of data collection begins with the date of data extraction for the first interim report.	Requested by the FDA
			Abstract as well as Sections 6, 9.2, and 9.4	Updated the IBD-PR launch date.	Launch date postponed
			Section 7.1	Updated the date of approval of etrasimod (Velsipity™) from December 2023 to October 2023.	Oversight
			Sections 9.2.1, 9.3.2, 9.7.1.4, 9.7.6, and Annex 1	Included participants with “Other and unspecified noninfective gastroenteritis and colitis” (ICD-10 K52) and	Addition of these participants was requested by the FDA

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				"Indeterminate colitis" (ICD-10 K52.3). The analysis of these participants will be separate from the main analysis for primary and secondary outcomes (as noted by footnote 1) and edits in section 9.7.6.	
			Section 9.2.1 and Annex 1	Updated age range of participants from 18 and over at enrollment to 18 to 50 years of age at enrollment.	Update requested by the FDA
			Section 9.7.3 (Table 4)	Added footnote to Table 4 to clarify the calculation for the etiologic periods.	Requested by the FDA
1.0	18 February 2025	Substantial	Section 9.2.2	Revised the exclusion criteria to allow for patients exposed to other S1P therapies (other than etrasimod) during pregnancy if their treatment on the other S1P therapy began ≥7 days (i.e., 5 half-lives of etrasimod) from the end of etrasimod treatment.	Requested by the FDA
			Section 9.3.5	Updated the list of concurrent maternal medical conditions to include heart disease, pulmonary disease, kidney disease, and liver disease (including but not limited to hepatitis).	Requested by the FDA
			Section 9.3.5	Updated the term "preterm labor" to "preterm birth" for consistency.	Oversight
			Section 9.4	Updated the definition for the "end of the second trimester" as "(around 26 to $27^{6/7}$ weeks)" to be more specific.	Requested by the FDA
			Section 9.5.3 (Table 3)	Corrected the value in the row titled "Infant developmental delay," under the column "4.5," from "71" to "21."	Requested by the FDA
			Section 9.5.3 (Tables 2 and 3)	Updated the prevalence estimate, reference, time frame for prevalence	Request by the FDA to review the prevalence

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				calculation, and corresponding sample size needed per cohort for SAB.	estimates used for sample size computation to align with the estimates used in Pfizer's pregnancy database study
			Section 9.7	Corrected from "a SAP" to "an SAP" to ensure correct grammar.	Oversight
			Section 9.7.4.2	Added marginal structural model text.	To account for possible effects of exposure to other S1P therapies, which was requested by the FDA
			Section 9.7.4.1	Added "Categorical variables with empty or near empty cells may be coalesced, binary variables with near-empty cells will be flagged for investigation."	Oversight
			Section 9.7.5	Updated the subgroups for "maternal age at conception."	Updated due to maximum age of 50 added to enrollment criteria
			Section 9.7.7	Added a sensitivity analysis to investigate the possibility of unmeasured confounding using E-values.	Requested by the FDA
			Section 9.7.8	Added a tipping point sensitivity analysis if the amount of missing data is greater than 10% for any of the variables in the models generated.	Requested by the FDA
1.0	18 Februar y 2025	Substantial	Section 12	Updated text to include multiple interim reports.	Requested by the FDA
			Section 13	Added new references.	As a result of updating information throughout the protocol
			Annex 1	Removed direct-to-HCP outreach.	Oversight

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			Annex 1	Added a list of the data points that will be collected for each of the data elements.	Requested by the FDA
			Annex 1	Added details for HCP follow-up to reduce the number of participants who are lost to follow-up.	Requested by the FDA
			Annex 2	Removed lamotrigine, dolutegravir, and clorazepate from the list of teratogens. Removed duplicates of bevacizumab and bortezomib. Reviewed and revised the list of teratogens, their half-life, pre-conception window exposure, and relevant exposure window.	Requested by the FDA
2.0	23 April 2025	Substantial	Annex 1	Re-added direct-to-HCP outreach	To maximize enrollment
			Section 9.5.2, Table 2	Update sample size estimations per cohort for SAB, gestational diabetes, pregnancy-induced hypertension, placental abruption, infant hospitalization, infant infections (serious and non-serious) and infant death using the Wilson (score) method, as indicated in footnote 2	To correct the error where the Clopper-Pearson exact method was used
			Section 9.5.3, Table 3	Update sample size estimations for SAB, gestational diabetes, pregnancy-induced hypertension, placental abruption, infant hospitalization, and infant death using SAS software	To correct the error where PASS software was used
			Section 4, Section 6, Section 9.2, Section 9.4	Update with actual dates of IBD-PR launch and first participant enrollment	These dates are now known (rather than estimated)
3.0	01 August 2025	Substantial	Section 9.2.1, Annex 1	Update the inclusion criterion regarding age from “18 to 50 years of age at enrollment” to “15	Requested by the FDA to account for potential off label use of etrasimod

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				to 50 years of age at enrollment"	
			Section 9.2.2	Removal of the exclusion criterion "Exposure to S1P therapies (other than etrasimod) <7 days from the end of etrasimod treatment during pregnancy"	Requested by the FDA to attempt to increase sample size
			Section 9.5.3	Update the stillbirth prevalence from 0.596% to 0.5% and corresponding reference in Table 2 and Table 3. Time frame for prevalence calculation, denominator from literature and sample size were updated accordingly.	To correct and align stillbirth prevalence estimate with a reference from prior FDA guidance
3.0	01 August 2025	Substantial	Section 9.5.3	Update to the preterm birth prevalence from 8.47% to 8.71% and corresponding reference in Table 2 and Table 3. Time frame for prevalence calculation and sample size were updated accordingly.	Updated preterm birth prevalence estimate based on more recently published data
			Section 9.7.1.7	Addition of a new section in data analysis to address exposure to S1P therapies other than etrasimod during the outcome ascertainment window.	As a result of removing the S1P exclusion criteria, analytic exclusions will be imposed to ensure other S1P therapies are excluded from the etrasimod-exposed and the etrasimod-unexposed cohorts during the predefined exposure window for a given outcome of interest
			Table 4	Update "relevant etiologic window" to "relevant outcome ascertainment window" in the header of the last column in Table 4. Updated the numerator for infant hospitalization,	To align terminology with the database protocol (C5041042)

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				serious infant infections, non-serious infant infections, and infant death to include the phrase “until 1 year after the full pregnancy exposure window”. Updated Footnote 1 to add “The exposure period starts 7 days prior to the date of conception and ends at the time of the pregnancy outcome” and to define each of the exposure windows.	
			Section 9.7.4.2	Section deleted, as participants exposed to S1P during pregnancy will be evaluated on a case-by-case basis and removed from the analysis for specific outcomes, as detailed in new Section 9.7.1.7.	As a result of removing the S1P exclusion criteria, analytic exclusions will be imposed to ensure other S1P therapies are excluded from the etrasimod-exposed and the etrasimod-unexposed cohorts during the predefined exposure window for a given outcome of interest
3.0	01 August 2025	Substantial	Section 9.7.5	Addition of a subgroup analysis for participants ages 18 to 50 years at enrollment. The maternal age group at conception categories were also updated to add the category of 15 to <18 years.	To retain analyses among 18-50-year--olds, consistent with the indicated population specified in the etrasimod label
			Annex 1	Addition of the exclusion criterion from IBD-PR: “exposure to methotrexate during pregnancy”.	To correct an accidental omission in previous versions
4.0	23 January 2026	Substantial	General	Protocol section numbering was updated following removal of numbering from the table of contents, resulting in renumbering of	Sponsor protocol template update

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				subsequent sections and minor formatting changes.	
			Study Information (Title page)	Added EU PAS register number once it became available.	The EU PAS Register number was unavailable in the prior version and has been added now that registration is complete and data collection has commenced
			Study Information, Section 2 Abstract	Removed Diego Wyszynski from list of Authors and list of Responsible Parties.	Author/Investigator is no longer responsible for the study (no longer with PPD) and not contactable
			Abstract, Sections 8.1, 8.3.4 (Table 1), 8.3.5, 8.5.2.2 (Tables 2 and 3), 8.7.3 (Table 4)	Replaced “pregnancy-induced hypertension” with “gestational hypertension” throughout.	To conform with terminology listed in ACOG guidelines, as requested by the FDA
4.0	23 January 2026	Substantial	Abstract, Section 8.5.2	Added section 8.5.2 to clarify the target sample size for the study. Updated sample size section of abstract for clarity.	Revised in response to FDA request to clarify the sample size target the study aims to achieve
			Abstract	Minor revisions to data analysis section.	Revised to be consistent with the data analysis section of the protocol
			Section 8.3.4 (Table 1)	Minor revision to additional ascertainment information for MCM.	Revised for clarity
			Section 8.3.5	Revised covariates list to include all covariates listed in the IBD-PR registry.	Revised to be consistent with the PASS SAP and IBD-PR registry
			Section 8.7.3 (Table 4)	Split last column, labeled “Relevant Outcome Ascertainment Window (Timing of Exposure	Revised to align with the database study protocol in

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				Assessment)" into two separate columns: "Relevant Outcome Ascertainment Window" and "Timing of Exposure Assessment." Updated Timing of Exposure column and Relevant Ascertainment Window cell contents to align with database study protocol. Updated footnote 1 for correctness.	response to FDA request
			Section 8.7.7	Added a sensitivity analysis restricting the denominator to pregnancies with at least 20 weeks gestation for outcomes that would not be diagnosed prior to 20 weeks' gestation (stillbirth, pre-eclampsia, eclampsia, gestational hypertension, placental abruption).	Revised in response to FDA request to include a sensitivity analysis with the denominator restricted to pregnancies with at least 20 weeks' gestation
4.0	23 January 2026	Substantial	Section 8.7.7	Added sensitivity analysis expanding the definition of the main analysis set to include participants who have self-reported (but not necessarily HCP-confirmed) exposure, UC diagnosis, and/or pregnancy confirmation.	To maximize the amount of relevant data presented to the FDA by including participants without HCP confirmation in sensitivity analyses
			Section 8.7.8	Removed mention of analysis listings.	In this structured data analysis study, data will be derived from the IBD-PR that exist as structured data by the time of study start. Individual patient data will not be collected as part of the PASS
			Annex 1	Added Maternal Health Form to Table 5 as an additional data collection form. No additional data are collected beyond what is already listed in the protocol.	This form was inadvertently omitted from earlier protocol versions

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ACOG = American College of Obstetricians and Gynecologists; EU PAS = European Union Post-Authorisation Study; FDA = Food and Drug Administration; HCP = healthcare provider; IBD-PR = CorEvitas Inflammatory Bowel Disease Pregnancy Registry; ICD = International Classification of Diseases; MCM = major congenital malformation; N/A = not applicable; PASS = post-authorization safety study; S1P = sphingosine 1-phosphate; SAB = spontaneous abortion; SAP = statistical analysis plan, UC = ulcerative colitis.

5. MILESTONES

Milestone	Planned Date
Registration in the HMA-EMA Catalogues of RWD studies	Prior to start of data collection
Start of data collection[1]	30 September 2025
End of data collection[2]	30 September 2032
Interim report #1	28 February 2026
Interim report #2	28 February 2027
Interim report #3	28 February 2028
Interim report #4	28 February 2029
Interim report #5	28 February 2030
Interim report #6	28 February 2031
Interim report #7	28 February 2032
Final study report	30 September 2033

HMA-EMA = Heads of Medicines Agencies-European Medicines Agency; RWD = Real-world data.
1 The study will use secondary data collected for the IBD-PR (CorEvitas Inflammatory Bowel Disease Pregnancy Registry). The start of data collection is defined as the date of data extraction for the first interim report. The date of IBD-PR launch is 19 March 2025, and first participant enrolled on 09 April 2025.
2 The end of data collection is defined as the date of data extraction for the final report.

6. RATIONALE AND BACKGROUND

6.1. Etrasimod

In October 2023, the United States (US) Food and Drug Administration (FDA) approved etrasimod (Velsipity™) for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) (FDA 2023). Etrasimod is a potent, orally bioavailable sphingosine 1-phosphate (S1P) receptor modulator that selectively activates S1P receptor subtypes 1, 4, and 5, with no detectable activity on $S1P_{2,3}$.

There are limited data on the safety of etrasimod use during pregnancy. Available data from reports of pregnancies from the etrasimod clinical development program are insufficient to identify a drug-associated risk of major birth defects, spontaneous abortion (SAB), or other adverse maternal, fetal, or infant outcomes (Velsipity™ USPI 2023); however, the S1P receptor plays an important role in embryogenesis, including vascular and neural development (Mendelson 2014).

6.2. Study Rationale

Due to limited human data, the US FDA issued postmarketing requirement for a pregnancy exposure registry. This study will address the gap in information on the safety of etrasimod when used in pregnancy in terms of risk of maternal, fetal, and infant outcomes. This non- interventional study is designated as a post-authorization safety study (PASS) and is a postmarketing requirement of the FDA.

7. RESEARCH QUESTION AND OBJECTIVES

The research question is: Is there an increased risk of adverse maternal, fetal, or infant outcomes among individuals who are exposed to etrasimod during pregnancy?
The primary objective of the study is to estimate the prevalence of major congenital malformations (MCMs) among individuals with moderate-to-severe UC who are exposed to etrasimod during pregnancy.
The secondary objectives of the study are:

- To estimate the prevalence of other maternal, fetal, and infant outcomes among pregnant individuals with moderate-to-severe UC who are exposed to etrasimod during pregnancy
- To contextualize the prevalence of outcomes among pregnant individuals who are exposed to etrasimod during pregnancy, estimate the prevalence of all outcomes of interest among pregnant individuals with moderate-to-severe UC who are not exposed to etrasimod during pregnancy
- If sample size permits, to estimate risk ratio (RR) for each study outcome comparing the outcomes of pregnant individuals with moderate-to-severe UC who are exposed to etrasimod with those who are not exposed to etrasimod

8. RESEARCH METHODS

8.1. Study Design

This observational cohort study aims to estimate the prevalence of maternal, fetal, and infant outcomes among individuals with moderate-to-severe UC who are exposed to etrasimod during pregnancy. The primary outcome of interest is MCMs. The maternal and pregnancy secondary outcomes include minor congenital malformations, pre-eclampsia, eclampsia, SABs, stillbirths, pregnancy terminations, preterm births, small for gestational age, gestational diabetes, gestational hypertension, and placental abruption. The infant secondary outcomes during the first year of life include postnatal growth deficiency, infant developmental delay, infant hospitalization, infant infections (both serious and non-serious), and infant death.
The study population will include two cohorts of pregnant individuals: one cohort of individuals with a diagnosis of moderate-to-severe UC who are exposed to etrasimod at any time during pregnancy and one cohort of individuals with a diagnosis of moderate-to-severe UC who are not exposed to etrasimod during pregnancy. The study will use secondary data collected for the IBD-PR, a prospective pregnancy registry based in the US and Canada.

8.2. Setting

The IBD-PR will launch after institutional review board (IRB) approval of the IBD-PR protocol. This PASS will use data that are collected as part of the IBD-PR. The IBD-PR launched on 19 March 2025; and as described in Section 5, the end of data collection for this study, which is defined as the date when data extraction for the final study report is available for analysis, is expected in September 2032.

8.2.1. Inclusion Criteria

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

1. A resident of the US or Canada
2. Enrolled in the IBD-PR, for which the following inclusion criteria apply:
    a. Currently pregnant
    b. 15 to 50 years of age at enrollment
    c. Diagnosis of an inflammatory bowel disease, including UC, Crohn’s disease, other and unspecified noninfective gastroenteritis and colitis (ICD-10 K52), or indeterminate colitis (ICD-10 K52.3)
    d. Evidence of a personally signed and dated informed consent document or, upon waiver of written consent by the relevant IRB/independent ethics committee, verbal consent, indicating that the individual (or a legally acceptable representative) has been informed of all pertinent aspects of the study
    e. Authorization for their healthcare provider (HCP) to provide data to the registry
    f. Contact information is available (for participant and HCPs)
3. Etrasimod-exposed cohort: exposure to etrasimod during pregnancy

4. Etrasimod-unexposed cohort: diagnosis of moderate-to-severe UC at conception[1]

The precise definition of “during pregnancy” is provided in Section 8.3.1.

8.2.2. Exclusion Criteria

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

1. Exposure to methotrexate during pregnancy
2. Etrasimod-unexposed cohort: exposure to etrasimod during pregnancy

8.3. Variables

Variables for the exposures, outcomes, demographics, and clinical characteristics of interest are included below. Data on these variables will be collected via maternal and HCP data collection forms in accordance with the procedures established for the IBD-PR. Details on the collection of each datapoint, including reporter(s), timepoint(s) for collection, and format of question/item, will be outlined in the statistical analysis plan (SAP).

8.3.1. Pregnancy Period

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

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

- First day of LMP, defined as $0^{0/7}$ gestational weeks, will be calculated as EDD minus 280 days (40 weeks)
- Gestational age will be calculated as the number of weeks elapsed since the first day of LMP
    - Gestational weeks $0^{0/7}$ to $13^{6/7}$ will be considered the first trimester

[1] Participants diagnosed with other and unspecified noninfective gastroenteritis and colitis or indeterminate colitis will be analysed separately, as noted in section 8.7.6.

  - Gestational weeks $14^{0/7}$ to $27^{6/7}$ will be considered the second trimester
  - Gestational weeks $28^{0/7}$ to pregnancy outcome will be considered the third trimester
- Date of conception (DOC), defined as $2^{0/7}$ gestational weeks, will be calculated as first day of LMP plus 14 days (2 weeks).

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

8.3.2. Ulcerative Colitis

A diagnosis of moderate-to-severe UC is a condition for inclusion in the unexposed cohort and the main analysis population. The IBD-PR collects disease information, including diagnosis (i.e., UC, Crohn's disease, other and unspecified noninfective gastroenteritis and colitis or indeterminate colitis), date of diagnosis, disease severity (e.g., moderate, severe, or fulminant), and type/location (e.g., ulcerative proctitis, proctosigmoiditis, left-sided colitis, pancolitis) at enrollment and throughout pregnancy. Disease severity is based on the HCP's clinical assessment of the patient, and the data collected are limited to those recorded in the patient's medical record. From the collected data, disease activity index scores will be calculated. Further details will be provided in the SAP.

8.3.3. Exposure

Individuals will be considered exposed during pregnancy if at least one dose of a product is taken during pregnancy or up to at least 5 times the product's half-life prior to conception. Based on the half-life of etrasimod (approximately 30 hours), individuals will be considered exposed to etrasimod during pregnancy if a dose is taken within 7 days prior to conception. The IBD-PR collects detailed information on dose, route, frequency, dates/duration of exposure, and indication/reason for use at enrollment and throughout pregnancy. Exposure will be categorized by trimester of exposure, and timing of exposure will impact an individual's contribution to the analysis population for certain outcomes. For instance, for the analysis of MCM, only individuals with first trimester exposure to etrasimod will be included in the etrasimod-exposed cohort (Section 8.7.3).

8.3.4. Outcomes

Table 1 presents the definitions of the outcomes of interest. MCM is the primary outcome of interest, and all other outcomes are secondary. For outcomes not simply reported by the HCP on data collection forms, additional guidance on outcome ascertainment by the virtual registry coordinating center (VRCC) using the reported data is provided.

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Additional Information on Ascertainment
MCM	An abnormality of body structure or function that is present at birth, is of prenatal origin (i.e., birth defect), has significant medical, social, or cosmetic consequences for the affected individual, and typically requires medical intervention (CDC 2020)	The IBD-PR defines and codes MCMs with criteria specified by the CDC MACDP (CDC 2021). a) Exclusion criteria for analyses: To avoid misattribution of the malformation to the medication, MCMs not associated with medication exposure, such as chromosomal abnormalities, genetic syndromes, prematurity-related conditions in infants born at <36 gestational weeks (e.g., patent ductus arteriosus, patent foramen ovale, inguinal hernias, or undescended testes), and positional effects (e.g., hip dislocation due to breech position or abnormal skull shape due to crowding by multiple fetuses), will not be considered MCMs in the statistical analyses (Holmes 2011). b) Adjudication process: The IBD-PR engages a panel of two independent experts in clinical genetics and neonatology, blinded to exposure, to review all MCMs reported to the registry and classify them using the CDC's MACDP system. Additionally, the birth defect evaluators provide their opinions regarding the timing of the development of observed defects. If additional information is needed to aid in classification, the birth defect evaluators request additionalANNEX 1. IBD-PR ENROLLMENT AND DATA COLLECTION. These assessments are recorded in the database. If there is a discrepancy, a third expert independently reviews and codes the case, serving as tie breaker. These reviews occur soon after the MCM is reported. Additional reviews occur if new information is received for the case, and to evaluate whether there is a possible temporal association between exposure (to etrasimod) and the development of observed defects. Additionally, the IBD-PR Scientific Advisory Committee reviews all MCM cases reported to the registry and reaches consensus on the coding of each case.
Minor congenital malformation	An anomaly or abnormality of body structure that is	The IBD-PR defines and codes minor congenital malformations with criteria

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Additional Information on Ascertainment
	present at birth, is of prenatal origin (i.e., birth defect), poses no significant health problem in the neonatal period, and tends to have limited social or cosmetic consequences for the affected individual (CDC 2020)	specified as defined by CDC (CDC 2019). The same process for adjudicating MCMs is used to adjudicate minor congenital malformations.
SAB	An involuntary fetal loss or the expulsion of the products of conception occurring at <20 gestational weeks	Section 8.3.1 provides information on the methods used to calculate gestational age.
Pregnancy termination	A voluntary fetal loss or interruption of pregnancy that occurs for any reason, including but not limited to for the preservation of maternal health or due to fetal abnormalities	None
Pre-eclampsia	A disorder of pregnancy associated with new-onset hypertension, which occurs most often after 20 weeks of gestation and frequently near term, and proteinuria. Or, in the absence of proteinuria, it is defined as new-onset hypertension with the new onset of any of the following: • Thrombocytopenia: platelet count <100,000/mL • Renal insufficiency: serum creatinine concentrations >1.1 mg/dL or a doubling of the serum creatinine concentration in the absence of other renal disease • Impaired liver function: elevated blood concentrations of liver transaminases to twice normal concentration • Pulmonary edema • New-onset headache unresponsive to	None

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Additional Information on Ascertainment
	medication and not accounted for by alternative diagnoses or visual symptoms (ACOG 2020a)	
Eclampsia	New-onset tonic-clonic, focal, or multifocal seizures in the absence of other causative conditions such as epilepsy, cerebral arterial ischemia and infarction, intracranial hemorrhage, or drug use (ACOG 2020a)	None
Stillbirth	Involuntary fetal loss occurring at ≥20 gestational weeks or, if gestational age is unknown, a fetus weighing ≥350 g (ACOG 2020b)	Section 8.3.1 provides information on the methods used to calculate gestational age.
Preterm birth	A live birth occurring at <37 gestational weeks	Section 8.3.1 provides information on the methods used to calculate gestational age.
SGA	Birth weight <10th percentile for sex and gestational age using standard growth charts for full and preterm live-born infants (Battaglia 1967)	For the determination of SGA, the registry will utilize the sex-specific international growth reference standards from INTERGROWTH-21st for those born between 24$^{0/7}$ and 42$^{6/7}$ gestational weeks (Villar 2014; Villar 2016). The INTERGROWTH-21st standards are the latest available global reference standards, representing contemporary information from an international, multiethnic, diverse population, and have been specifically developed for modern research.
Postnatal growth deficiency	Weight, length, or head circumference in <10th percentile for sex and chronological age using standard growth charts	Postnatal growth deficiency, as part of routine care, will be evaluated at 4 and 12 months of infant age; deficiencies in weight, length, and head circumference will be evaluated separately. For the determination of postnatal growth deficiency, the registry will utilize the sex-specific international growth reference standards from the WHO for children ages 0 to 59 months. The WHO growth standards are recommended for use in the US for infants and children 0 to 2 years of age (CDC 2010).
Gestational diabetes	Any degree of glucose intolerance with onset or first	None

Table 1. Outcome Definitions and Ascertainment

Outcome	Definition	Additional Information on Ascertainment
	recognition during pregnancy (ADA 2004)	
Gestational hypertension	A disorder of pregnancy defined as a systolic blood pressure of 140 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 (ACOG 2020a)	None
Placental abruption	Premature separation of the placenta from its uterine attachment before the delivery of a fetus (Brandt 2023)	None
Infant developmental delay	Failure to achieve the developmental milestones for chronological age, as defined by the CDC (CDC 2023)	Infant developmental delay, as part of routine care, will be evaluated separately at 4 and 12 months of infant age for each CDC-defined category (social/emotional, language/communication, cognitive, and movement/physical development).
Infant hospitalization	Admission of an infant to a hospital	None
Infant infections (serious or non-serious)	Infant infections that resulted in medical visit or hospitalization	None
Infant death	Death of an infant before his or her first birthday	None

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

8.3.5. Covariates

The following variables, which are collected by IBD-PR (or derived from collected data), will be considered potential covariates:

- Maternal age at conception
- Calendar year at conception
- Country (i.e., US, Canada)
- Geographic region
- Maternal race

- Maternal ethnicity
- Maternal insurance status (commercial insurance, Medicaid insurance, or uninsured)
- Proxies for maternal socioeconomic status, including maternal education, employment status, and income
- Proxy for maternal prenatal care, including number of prenatal care visits and timing of first prenatal care visit
- Maternal pre-pregnancy body mass index, calculated from pre-pregnancy weight and height
- Gestational age at registry enrollment
- Gestational age at pregnancy outcome
- Method of conception
- Number of fetuses for current pregnancy
- Fetal/infant sex
- Concurrent maternal medical conditions, including thyroid abnormalities, infectious diseases, asthma, diabetes, hypertension, seizure disorder, autoimmune diseases, depression and other psychiatric disorders, heart disease, pulmonary disease, kidney disease, liver disease (including but not limited to hepatitis), sexually transmitted diseases, and uterine or cervical abnormalities (e.g., congenital uterine abnormalities)
- Concurrent pregnancy-related maternal medical conditions or pregnancy complications, including pre-eclampsia, eclampsia, gestational diabetes, gestational hypertension, preterm birth, and placental abruption
- Prenatal testing in current pregnancy, including whether any prenatal tests have been performed, name of test, type of test (diagnostic or screening), gestational age at test, and whether the test indicated any abnormal findings
- Number of previous pregnancies
- Previous pregnancy outcomes (spontaneous abortion, stillbirth, pregnancy termination, live birth)
- Previous pregnancy complications
- Characteristics of previous live births (preterm, small for gestational age [SGA])
- Previous fetus/infant with congenital malformations (major and minor)
- Family history of congenital malformations (major and minor)
- Characteristics of UC, including disease severity, type, and duration
- Maternal exposure to other drugs or biological products, including prescription and nonprescription drugs, dietary supplements including folic acid and prenatal vitamins, vaccines, teratogens, and investigational medications, during pregnancy and gestational age at exposure
- Maternal exposure to tobacco, alcohol, marijuana, or recreational or illicit drugs during pregnancy and timing of exposure

8.4. Data Sources

The study will use secondary data collected from the IBD-PR, a prospective pregnancy registry based in the US and Canada that launched in March 2025. The IBD-PR systematically collects data from enrolled pregnant individuals and their HCPs. Pertinent data documented in participants' medical records during medical care are collected. The assessment of pregnancy outcomes spans the entire gestational period, with data collection occurring at enrollment, end of the second trimester (around 26 to $27^{6/7}$ weeks), and at pregnancy outcome (live birth or fetal loss). Among live births, infant outcomes are evaluated at approximately 4 and 12 months of age. More information on the IBD-PR is provided in ANNEX 1.
In addition, the study may use background rates from population-based surveillance systems, other registries (e.g., existing disease registries), or the published literature to put prevalence estimates of the outcomes of interest into context.

8.5. Study Size

8.5.1. Assessment of Study Feasibility

To assess the feasibility of this study, the following data-based assumptions regarding the prevalence of UC, pregnancy, and etrasimod uptake were made to estimate the number of individuals who will potentially be exposed to etrasimod during pregnancy:

- The prevalence of UC was estimated to be 0.35% in two large US administrative databases between 2007 and 2016 (Ye 2020; Luther 2020)
- Among those with UC, the proportion of individuals with moderate-to-severe disease was assumed to be 19% (Lee 2020b)
- Among those with moderate-to-severe UC, the proportion of individuals who use pharmacotherapy for the treatment of UC was assumed to be 50% (Lee 2020a; Tripathi 2021)
- Among those with moderate-to-severe UC using pharmacotherapy, the proportion receiving etrasimod was assumed to be 10%

These assumptions were applied to the population of females of childbearing potential in the US (estimated to be 74,960,628 females aged 15 to 49 years; US Census 2021), which yielded 2,492 females of childbearing potential who will potentially receive etrasimod for the treatment of moderate-to-severe UC. After application of the general fertility rate in the US (56.0 births per 1,000 females aged 15 to 44 years; Osterman 2022), it was estimated that 140 live births may potentially be exposed to etrasimod in utero. Given the 3% MCM rate among live births (CDC 2008) in the US general population and assuming no increased risk of MCM with etrasimod, these 140 etrasimod-exposed live births can be expected to result in approximately four live births with MCMs.
If the study were to capture one-quarter, or 35, of the etrasimod-exposed live births, the study would be expected to capture approximately one live birth with MCMs.

8.5.2. Target Sample Size

The target sample size that the study aims to achieve is 364 pregnant participants in each of the two cohorts of the study population (for a total target sample size of 728 pregnant participants). This target sample size estimate is based on the comparative analyses and the methods and assumptions for this calculation are presented in 8.5.2.2. To perform the descriptive analyses alone , 400 participants (200 in each cohort) would be sufficient (Section 8.5.2.1).

8.5.2.1. Sample Size Estimation for Prevalence

Sample size calculations were performed with SAS® statistical software (version 9.4 or higher, SAS Institute, Cary, NC) and PASS 2021 Power Analysis and Sample Size software (version 21.0.3, CSS, LLC, Kaysville, Utah). For the calculations, general population prevalence estimates were obtained for the outcomes of interest from various sources, including the Metropolitan Atlanta Congenital Defects Program, National Vital Statistics System, and published literature.

Table 2 presents the sample size by outcome required to attain a range of prevalence precisions from 1% to 5%. Precision is calculated as the half-width of the two-sided 95% confidence interval (CI) using the Wilson (score) method for binomial proportions. As shown in Table 2, assuming a prevalence of MCM equivalent to 3% in each cohort (conservative approach), 145 live births in the analysis population of each cohort are needed to estimate the prevalence of MCM with ±3% precision.

To estimate the number of pregnancies that will need to be included to result in 145 live births (with first trimester exposure, if in the exposed cohort) in the analysis population per cohort, several factors were considered, including the expected proportion of live births in the study, the proportion of pregnancies with exposure to etrasimod in the first trimester, and the proportion of pregnancies expected to be excluded from the analysis population. Reasons for exclusion from the analysis population are provided in Section 8.7.1. It was assumed that 90% of pregnancies would be exposed in the first trimester, 90% of pregnancies would result in a live birth (Covington 2010; Veley 2020), and 10% of pregnancies would be excluded from the analysis population. Given these assumptions, to attain 145 live births per cohort, 200 pregnancies would need to be included in each of the two cohorts of the study population, and a minimum of 400 pregnancies would need to be included in the study. This sample size will enable the study to estimate the prevalence of MCM in each cohort with ±3% precision with 95% confidence. For outcomes with very low prevalence (e.g., eclampsia, stillbirth), the study will not be able to estimate prevalence with suitable precision.

8.5.2.2. Sample Size Estimation for Comparative Analyses

Table 3 presents the sample size needed to detect a range of RRs, by outcome. Using MCM as an example, 265 live births in the analysis population of each cohort are needed to detect a RR of 3.0. Given the same assumptions applied above, to attain 265 live births (with first trimester exposure, if in the exposed cohort) in the analysis population per cohort, 364 pregnancies would need to be included in each of the two cohorts of the study population, and a total of 728 pregnancies would need to be included in the study.

Table 2 Precision-based Sample Size Calculations

Outcome	Reference Prevalence[1]	Reference	Time frame for prevalence calculation	Denominator (From Literature)	Sample Size Needed per Cohort to Estimate Prevalence With Specified Precision[2]								
					1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%
MCM	3.0%	CDC 2008	2005	Live births	1,143	521	303	201	145	111	89	73	61
Pre-eclampsia	3.8%	Ananth 2013	2010	Pregnancies	1,423	642	369	242	173	131	103	84	70
Eclampsia	0.281%	Butwick 2020	2017	Live births	249	150	107	82	67	56	48	42	37
SAB	15.3%	Quenby 2021	2021	Pregnancies	4,978	2,213	1,245	797	553	407	311	246	199
Pregnancy termination	20.6%	Jones 2022	2020	Pregnancies	6,282	2,791	1,569	1,004	697	512	391	309	250
Stillbirth	0.5%	FDA 2002	2001	Pregnancies	305	173	119	90	72	59	51	44	39
Preterm birth	8.71%	Osterman 2025	2023	Singleton live births	3,059	1,362	768	493	344	254	195	155	127
SGA	10.0%	By definition, due to the normal distribution of infant size	N/A	Singleton live births	3,461	1,540	868	557	388	286	219	174	141
Gestational diabetes	7%	Diabetes care 2004	2004	Pregnancies	2508	1119	633	407	285	211	163	130	107
Gestational hypertension	13.0%	Ford 2022	2019	Pregnancies	4346	1932	1087	696	484	356	273	216	175
Placental abruption	0.6% to 1.2%	Brandt 2023	Article is 2023, cited from 67-91, 93, and 2006	Pregnancies	519	259	163	116	89	72	60	51	44
Postnatal growth deficiency	10.0%	By definition, due to the normal distribution of infant size	N/A	Singleton live births	3,461	1,540	868	557	388	286	219	174	141

Table 2 Precision-based Sample Size Calculations

Outcome	Reference Prevalence[1]	Reference	Time frame for prevalence calculation	Denominator (From Literature)	Sample Size Needed per Cohort to Estimate Prevalence With Specified Precision[2]								
					1%	1.5%	2%	2.5%	3%	3.5%	4%	4.5%	5%
Infant developmental delay	13%	Rosenberg 2008	2001	Live births	4,346	1,932	1,087	696	484	356	273	216	175
Infant hospitalization	12.1%	Iacobelli 2017	2011-2012	Live births	4088	1818	1023	656	456	335	257	203	165
Infant infections (serious and non-serious)	90.0%	Hyvönen 2023	2016-2018	Live births	3461	1540	868	557	388	286	219	174	141
Infant death	0.56%	CDC 2024	2022	Live births	322	179	122	92	73	60	51	44	39

CDC = Centers for Disease Control and Prevention; MCM = major congenital malformation; N/A = not applicable; SAB = spontaneous abortion; SGA = small for gestational age
1 Reference prevalence = prevalence of outcome in general population for pregnant individuals of any age.
2 Sample size calculations were performed in the post-authorization safety study software for the outcomes of interest; precision is calculated as the half-width of the two-sided 95% confidence interval using the Wilson (score) method for binomial proportions.

Table 3. RR-based Sample Size Calculations

Outcome	Prevalence in Unexposed	Reference	Time Frame for Prevalence	Denominator (From Literature)	Exposed: Unexposed Ratio	Sample Size Needed per Cohort to Detect Specified RR							
						1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
MCM	3.0%	CDC 2008	2005	Live births	1:1	2,627	796	413	265	190	146	117	97
Pre-eclampsia	3.8%	Ananth 2013	2010	Pregnancies	1:1	2,054	622	322	206	148	113	91	75
Eclampsia	0.281%	Butwick 2020	2017	Live births	1:1	28,973	8,824	4,600	2,961	2,130	1,640	1,322	1,101
SAB	15.3%	Quenby 2021	2021	Pregnancies	1:1	438	129	65	41	28	21	16	13
Pregnancy termination	20.6%	Jones 2022	2020	Pregnancies	1:1	300	87	43	26	18	13	9	-
Stillbirth	0.5%	FDA 2002	2001	Pregnancies	1:1	16,241	4,944	2,577	1,658	1,192	918	740	616
Preterm birth	8.71%	Osterman 2025	2023	Singleton live births	1:1	842	252	130	82	58	44	35	29
SGA	10.0%	By definition, due to the normal distribution of infant size	N/A	Singleton live births	1:1	721	215	110	70	49	37	29	24
Gestational diabetes	7%	Diabetes care 2004	2004	Pregnancies	1:1	1,071	322	166	106	75	57	46	38
Gestational hypertension	13.0%	Ford 2022	2019	Pregnancies	1:1	532	158	80	50	35	26	21	17
Placental abruption	0.6% to 1.2%	Brandt 2023	Article is 2023, cited from 67-91, 93, and 2006	Pregnancies	1:1	6,711	2,041	1,062	683	491	377	304	253
Postnatal growth deficiency	10.0%	By definition, due to the normal distribution of infant size	N/A	Singleton live births	1:1	721	215	110	70	49	37	29	24

Table 3. RR-based Sample Size Calculations

Outcome	Prevalence in Unexposed	Reference	Time Frame for Prevalence	Denominator (From Literature)	Exposed: Unexposed Ratio	Sample Size Needed per Cohort to Detect Specified RR							
						1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0
Infant developmental delay	13%	Rosenberg 2008	2001	Live births	1:1	532	158	80	50	35	26	21	17
Infant hospitalization	12.1%	Iacobelli 2017	2011-2012	Live births	1:1	579	172	88	55	39	29	23	18
Infant infections (serious and non-serious)	90.0%	Hyvönen 2023	2016-2018	Live births	1:1	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*	N/A*
Infant death	0.56%	CDC 2024	2022	Live births	1:1	14,491	4,411	2,299	1,479	1,063	819	660	549

CDC = Centers for Disease Control and Prevention; MCM = major congenital malformation; N/A = not applicable; RR = risk ratio; SAB = spontaneous abortion; SGA = small for gestational age
Note: Calculations used SAS software (version 9.4), Fisher's exact conditional test with Walters normal approximation method, assuming 80% power and 2-sided α of 0.05.
* N/A is indicated because, with a baseline frequency of 90.0%, it is not possible to achieve a risk ratio of 2x or higher.

8.6. Data Management

The study will be conducted using data collected for the IBD-PR. Data will be collected through streamlined data collection forms submitted by participants and HCPs. The database will be designed and maintained according to CorEvitas' standard data management procedures.
Data analyses for this study will be performed using the statistical software program SAS (version 9.4 or higher; SAS Institute, Cary, NC).

8.7. Data Analysis

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

8.7.1. Analysis Population

The analysis population will include pregnancies that:

- Are valid (Section 8.7.1.1)
- Are not exposed to teratogens or investigational medications (Section 8.7.1.2)
- Are not considered lost to follow-up (Section 8.7.1.3)
- Have a diagnosis of moderate-to-severe UC at conception (Section 8.7.1.4)

For the analyses of preterm birth, SGA, and postnatal growth deficiency, multiple-gestation pregnancies will be excluded from the analysis population (Section 8.7.1.5).

8.7.1.1. Valid Versus Invalid Pregnancies

A valid pregnancy will be defined as a pregnancy with sufficient data, submitted or confirmed by an HCP, for determining and meeting inclusion/exclusion into one of the study cohorts. Pregnancies that lack the minimum data required for determining inclusion or exclusion into one of the study cohorts or who lack confirmation of exposure, pregnancy, or UC diagnosis from an HCP will be considered invalid. Invalid pregnancies will be enumerated in each registry report but will not be included in statistical analyses.

8.7.1.2. Pregnancies Exposed to Known Teratogens or Investigational Medications

Pregnancies will be considered exposed to teratogens or investigational medications if a dose is taken at any time during pregnancy (from conception to pregnancy outcome) or prior to pregnancy (time period equivalent up to at least 5 times the product's half-life). A list of known teratogens (ANNEX 2) has been developed and will be continually updated based on the data available in the Teratogen Information System (TERIS) database of teratogenic agents and publications (Polifka 2002; Feldkamp 2015; Zomerdijk 2015; TERIS 2021). Investigational medications include drugs that are not yet approved by the FDA. Pregnancies that are exposed to known teratogens or investigational medications will be excluded from the analysis population but will be included in supplementary analyses.

8.7.1.3. Pregnancies Lost to Follow-up

A pregnancy will be considered lost to follow-up if follow-up information is never obtained or is unavailable; pregnancies without pregnancy outcome information will be considered pregnancies lost to follow-up, and live-born infants without follow-up data after birth will be

considered infants lost to follow-up. Information from pregnancies lost to follow-up (e.g., demographic characteristics, abnormal prenatal test results, and reason for loss to follow-up, if available) will be summarized in each registry report, but these pregnancies will be excluded from the analysis population. While infants who are lost to follow-up will not contribute to the analysis of infant outcomes after the point in which they were lost to follow-up, the pregnancy information from their mothers will be included in the analysis of pregnancy outcomes. In addition, the proportion of pregnancies that are lost to follow-up will be compared between the cohorts to assess any potential differential loss to follow-up that could bias the comparative analyses.

8.7.1.4. Diagnosis of Moderate-to-Severe UC

As shown in Section 8.2.1, the IBD-PR enrolls pregnant individuals diagnosed with inflammatory bowel diseases, including UC, Crohn's disease, other and unspecified noninfective gastroenteritis and colitis, or indeterminate colitis. For this study, participants who are enrolled in the IBD-PR and exposed to etrasimod during pregnancy are eligible for inclusion in the enrolled population, regardless of their IBD diagnosis or severity; however, the analysis population will be limited to those participants who have a diagnosis of moderate-to-severe UC. Those excluded from the analysis population will be included in supplementary analyses, and their characteristics will be provided in study reports.

8.7.1.5. Multiple-Gestation Pregnancies

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

8.7.1.6. Subsequent Pregnancies

Individuals may contribute multiple pregnancies to the analysis population during the study observation period. Statistical nonindependence due to multiple pregnancies from the same individual will be addressed in the analysis.

8.7.1.7. Pregnancies Exposed to S1P Therapies (Other Than Etrasimod)

Participants exposed to S1P therapies (other than etrasimod) will be excluded from the analysis population on a per-analysis basis, depending on the relevant ascertainment window (Table 4) for that analysis. For each outcome, participants will be excluded from the analysis if their exposure to S1P therapies (other than etrasimod) is during the ascertainment window for that outcome. However, they may also be excluded if the exposure is within 5 half-lives prior to the ascertainment window. Additional details will be outlined in the SAP.

8.7.2. Descriptive Characteristics

Participant characteristics (including the covariates listed in Section 8.3.5) will be summarized with descriptive statistics for each cohort.
The number of observations, median, mean, standard deviation, minimum, and maximum will be reported for each continuous variable. The frequency and percentage per category will be reported for each categorical variable.
If adequate sample size is achieved for comparative analyses (see Section 8.5.2.2), balance between the cohorts will be assessed by calculating the standardized mean differences for all covariates, comparing the etrasimod-exposed and etrasimod-unexposed cohort. These

standardized mean differences will be presented before and after inverse probability of treatment weighting (IPTW).

8.7.3. Outcome Prevalence

Prevalence of the outcomes of interest will be calculated according to the conventions described in **Table** 4. In general, the prevalence of each outcome will be calculated by dividing the number of cases of the outcome by the appropriate denominator for that particular outcome, based on clinical knowledge.

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

Table 4. Outcome Prev valence Calculations

Outcome	Numerator (Among Those in Denominator)	Denominator	Relevant Outcome Ascertainment Window 1	Timing of Exposure Assessment1
MCM	Live births with confirmed (i.e., adjudicated) MCMs (excluding MCMs not associated with medication exposure)	Live births	Up to 365 days after birth	First trimester exposure window
MCM sensitivity analysis (see Section 8.7.7)	Live births and fetal losses with confirmed MCMs (excluding MCMs not associated with medication exposure)	Live births and fetal losses	Up to 365 days after birth (live births) or up to 30 days after delivery (fetal loss)	First trimester exposure window
Minor congenital malformations	Live births with minor congenital malformation	Live births	Up to 365 days after birth	Pregnancy exposure window
Pre-eclampsia	Pregnancies with pre-eclampsia	Pregnancies with pregnancy outcome data	≥20 completed weeks of gestation	Pregnancy exposure window
Eclampsia	Pregnancies with eclampsia	Pregnancies with pregnancy outcome data	≥20 completed weeks of gestation	Pregnancy exposure window

Table 4. Outcome Prev valence Calculations

Outcome	Numerator (Among Those in Denominator)	Denominator	Relevant Outcome Ascertainment Window 1	Timing of Exposure Assessment1
SAB	Spontaneous abortions	Pregnancies with pregnancy outcome data that are enrolled in IBD-PR prior to 20 gestational weeks	<20 completed weeks of gestation	20-week exposure window
Pregnancy termination	Pregnancy terminations	Pregnancies with pregnancy outcome data	From DOC through 30 days after pregnancy end date	Pregnancy exposure window
Stillbirth	Stillbirths	Pregnancies with pregnancy outcome data	≥20 completed weeks of gestation	Pregnancy exposure window
Preterm birth	Preterm births	Singleton live births without confirmed MCM among pregnancies that are enrolled prior to 37 gestational weeks	<37 completed weeks of gestation	37-week exposure window
Gestational diabetes	Pregnancies with gestational diabetes	Pregnancies with pregnancy outcome data	LMP through pregnancy outcome	Pregnancy exposure window
Gestational hypertension	Pregnancies with gestational hypertension	Pregnancies with pregnancy outcome data	≥20 completed weeks of gestation	Pregnancy exposure window
Placental abruption	Pregnancies with placental abruption	Pregnancies with pregnancy outcome data	≥20 completed weeks of gestation	Pregnancy exposure window
SGA	SGA births	Singleton live births without confirmed	Up to 30 days after delivery	Pregnancy exposure window

Table 4. Outcome Prev valence Calculations

Outcome	Numerator (Among Those in Denominator)	Denominator	Relevant Outcome Ascertainment Window 1	Timing of Exposure Assessment1
		MCM with weight data		
Postnatal growth deficiency (at 4 and 12 months)	Infants with postnatal growth deficiency	Singleton live births without confirmed MCM, preterm birth, or SGA with weight/length/ head circumference data at the specified timepoint	Up to the 12-month well-baby check-up	Pregnancy exposure window
Infant developmental delay (at 4 and 12 months)	Infants with developmental delay	Live births without confirmed MCM or preterm birth with developmental milestone data for the category at the specified timepoint	Up to the 12-month well-baby check-up	Pregnancy exposure window
Infant hospitalization	Infants with hospitalization until 1 year after the full pregnancy exposure window	Live births without confirmed MCM or preterm birth with developmental milestone data for the category at the specified timepoint	Up to 12 months after birth	Pregnancy exposure window
Serious infant infections	Infants with serious infections until 1 year after the full pregnancy exposure window	Live births without confirmed MCM or preterm birth with developmental milestone data	Up to 12 months after birth	Pregnancy exposure window

Table 4. Outcome Prev valence Calculations

Outcome	Numerator (Among Those in Denominator)	Denominator	Relevant Outcome Ascertainment Window 1	Timing of Exposure Assessment1
		for the category at the specified timepoint		
Non-serious infant infections	Infants with non-serious infections until 1 year after the full exposure window	Live births without confirmed MCM or preterm birth with developmental milestone data for the category at the specified timepoint	Up to 12 months after birth	Pregnancy exposure window
Infant death	Infants who die until 1 year after the full pregnancy exposure window	Live births without confirmed MCM or preterm birth with developmental milestone data for the category at the specified timepoint	Up to 12 months after birth	Pregnancy exposure window

DOC = date of conception; IBD-PR = CorEvitas Inflammatory Bowel Disease Pregnancy Registry; LMP = last menstrual period; MCM = major congenital malformation; SAB = spontaneous abortion; SGA = small for gestational age
1 The pregnancy exposure window starts 7 days prior to the date of conception and ends at the time of the pregnancy outcome. Gestational weeks and (<20, ≥ 20, <37) are calculated from the first day of LMP (Section 8.3.1).

8.7.4. Comparative Analyses

Comparative analyses will be conducted for each outcome if sample size permits. Crude (unadjusted) RRs (and corresponding 95% Cis) will be calculated using Exact methods. Adjusted RRs will be calculated using generalized linear models (binomial family) with a log (RR) link and weighted by IPTW (Desai 2019). The covariates that will be potentially included in the models are listed in Section 8.3.5. The SAP will include detailed information on covariate selection, which will be based on expert clinical input. If model convergence issues arise, variables may be removed from the model in a pre-specified order. The Clopper-Pearson method will be used to derive 95% CIs.

8.7.4.1. Propensity Score Modeling

IPTW will be calculated using propensity scores estimated from propensity score models (Desai 2019). Each individual's propensity score (the probability of being in the exposed cohort, given membership in the study population [either cohort]) will be estimated using a logistic regression model with exposure status as the outcome (dependent variable). The covariates listed in Section 8.3.5. will be considered for inclusion in the model as independent (predictor) variables. Each variable will be carefully considered by the investigators to ensure that only potential risk factors (and therefore potential confounders) for the study outcomes are included in the final propensity score model. As discussed in Section 8.7.8, if there is a high degree of missing covariate data (>10%), multiple imputation may be considered to minimize the loss of observations in the analysis. Further details will be provided in the SAP. Categorical variables with empty or near empty cells may be coalesced; binary variables with near-empty cells will be flagged for investigation.
Each individual's propensity score will be used to create a weight that is equal to the inverse probability of receiving treatment (in this case, being in the etrasimod-exposed cohort or etrasimod-unexposed cohort). Stabilized weights will be estimated with trimming at the first and 99th percentiles to minimize the impact of any extreme weights (Stuart 2010; Hernán 2020).

8.7.5. Subgroup Analyses

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

- Timing of exposure (earliest trimester of exposure)
- Extent of exposure (cumulative dose during pregnancy)
- Duration of exposure (cumulative duration during pregnancy or relevant exposure window)
- Maternal age group at conception (15 to <18, 18 to 30, >30 to 40, and >40 to 50 years)
- UC severity (moderate, severe, fulminant)
- Participants aged 18 to 50 years at enrollment. This is to account for the per-label use of etrasimod as indicated for patients 18 to 50 years who may become pregnant and may be prescribed etrasimod.

Further analyses may be conducted to assess the sensitivity of subgroup analyses or to investigate inconsistencies between subgroups and the pooled population.

8.7.6. Supplementary Analyses

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

- Exposure to a known teratogen or an investigational medication during or prior to pregnancy (teratogen/investigational medication-exposed pregnancies)
- Diagnosis other than moderate-to-severe UC (including other and unspecified noninfective gastroenteritis and colitis or indeterminate colitis)

8.7.7. Sensitivity Analyses

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

- A sensitivity analysis of MCM will be conducted that applies a stricter definition of prospective enrollment. For this analysis, pregnancies that enroll in IBD-PR prior to diagnostic prenatal testing will be considered prospectively enrolled, and pregnancies that enroll after diagnostic prenatal testing, regardless of the results, will be considered retrospectively enrolled. The outcomes of pregnancies that enroll prior to diagnostic prenatal testing will be compared with those of pregnancies that enrolled after diagnostic prenatal testing
- As described in Table 4, a sensitivity analysis will be conducted that broadens the MCM denominator to include fetal losses in addition to live births
- A sensitivity analysis will be conducted for outcomes that are only diagnosed at 20 weeks or later in pregnancy (stillbirth, pre-eclampsia, eclampsia, gestational hypertension, placental abruption). The analysis set for these outcomes will be restricted to participants who reached at least 20 weeks of gestation during their pregnancy.
- The main analysis set excludes participants who do not have HCP-confirmed pregnancy status, exposure and/or UC diagnosis. A sensitivity analysis will be conducted that includes participants with self-reported (but not necessarily HCP-confirmed) exposure, UC diagnosis, and/or pregnancy confirmation.
- The etrasimod-unexposed cohort will be restricted to the subset of pregnancies exposed to at least one UC therapy. If sample size permits, the cohort may be further restricted to pregnancies exposed to other advanced therapies for UC (i.e., small molecules and biologics)
- To investigate the possibility of unmeasured confounding, we will use E-values to determine the minimum strength of an association that unmeasured confounder would need to affect any observed association. While E-values have key important limitations (specifically, they do not provide information about specific confounders), they provide important information about the robustness of the modeled association to the potential unmeasured confounders.

8.7.8. Missing Data

The frequency and percentage of pregnancies with missing data will be presented for each variable. If the proportion of missing data is large (>10%), missing data methods, such as multiple imputation, may be considered. In addition, start and end dates of medical conditions or exposures where the month and year are known but the day is missing will be imputed for analyses. Missing start dates will be set to the first day of the month, and missing end dates will be set to the last day of the month.
As a sensitivity analysis, if the amount of missing data is greater than 10% for any of the variables in the model, a tipping point analysis will also be conducted. For the tipping point analysis, missing data will be imputed, using multiple imputation, for the variables with substantial missing data using a range of scenarios for the exposure effect. In addition, robustness checks will be conducted on subsets of the data after multiple imputation. The results from both the complete-case analysis and the robustness checks after multiple imputation will be reported along with the study results.

8.8. Quality Control

For the IBD-PR, ensuring high quality data is an ongoing, multistep process involving automatic programming of edit checks for critical data variables in the electronic data capture system as well as visual review for completeness, logic, consistency, and accuracy by the VRCC staff. As recommended in regulatory guidance documents, data collection forms are carefully designed to ensure data quality and integrity. All participant-reported data are verified by the appropriate HCP, where possible.

8.9. Limitations of the Research Methods

This secondary data collection study uses data from the IBD-PR. The IBD-PR collects data prospectively, minimizing the potential impact of recall bias. With primary data collection, rich, detailed information can be collected on participants, their pregnancies, and their infants, including information that is not routinely captured in medical records. Furthermore, direct data capture from participants and HCPs may minimize potential exposure, outcome, and covariate misclassification. Nonetheless, this study is subject to several limitations.
Many individuals avoid medications during pregnancy and the safety of etrasimod use in pregnancy is currently unknown. Hence, the number of enrolled etrasimod-exposed participants may be small, precluding the ability to calculate RRs or derive meaningful conclusions.
Although the IBD-PR aims to enroll individuals prospectively and early in their pregnancies, reducing the potential for recall and selection bias, early pregnancy losses may be less likely to be captured by the registry. Indeed, research suggests that 90% of pregnancies enrolled in registries result in a live birth (Covington 2010; Veley 2020) whereas national estimates suggest up to 28% of pregnancies end in early losses (i.e., approximately 70% result in a live birth) (Rossen 2018).
As with any voluntary study, the IBD-PR is prone to selection bias (e.g., high- or low-risk individuals may be more likely to enroll). A description of participant characteristics including comorbidities and pregnancy history will help assess the extent of such possible bias.
Some outcome risk factors may be unbalanced between the exposed and unexposed study cohorts. Propensity scores will be employed to statistically adjust for any baseline differences between cohorts. However, only measured covariates will be factored into the analysis and the potential for residual confounding remains due to unmeasured or poorly measured confounders.
The primary outcome, MCM, is a heterogeneous composite of any type of MCM. Individual drugs are more likely to have effects on specific MCM subtypes than all MCMs. However, the study is not powered to detect increases in the risk of individual defects.
While a sensitivity analysis is planned to assess the occurrence of MCMs in fetal losses, the condition of the lost fetus and the exact nature of MCM may be unknown. The IBD-PR retrieves any information available, but this information is expected to be limited.

8.10. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN PARTICIPANTS

9.1. Participant Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

9.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by the Sponsor is not required.

9.3. Institutional Review Board/ Ethics Committee

It is the responsibility of the IBD-PR to have prospective approval of the study protocol, protocol amendments, materials describing the consent process (e.g., statement regarding agreement to participate), and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/ethics committee (EC). All correspondence with the IRB/EC should be retained by IBD-PR. Copies of IRB/EC approvals should be forwarded to the Sponsor.

9.4. 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 guidelines:

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

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study will involve data derived from the IBD-PR that exist as structured data by the time of study start. In this structured pregnancy database, individual patient data will not be retrieved or validated, and it will not be possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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 CorEvitas is aware of any new information which might influence the evaluation of the benefits and risks of a Sponsor product, the Sponsor should be informed immediately.
In addition, CorEvitas will inform the Sponsor immediately of any urgent safety measures taken by the registry to protect the study participants against any immediate hazard, and of any serious breaches of this noninterventional study protocol of which CorEvitas becomes aware.
Interim study reports and a final study report will be submitted to the FDA. Conference abstracts and manuscripts based on specific endpoints of interest may be developed for publication purposes. Additionally, this study will be disclosed and registered in the Heads of Medicines Agencies-European Medicines Agency (HMA-EMA) Catalogues of real-world data sources and studies.

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ANNEX 1. IBD-PR ENROLLMENT AND DATA COLLECTION

Enrollment

A multimodal approach is used to deliver registry education and recruitment materials to targeted healthcare providers (HCPs) and patients. This approach involves direct-to-HCP outreach to increase awareness of the registry as well as online and print advertising directed to HCPs and patients.
The virtual registry coordinating center (VRCC) coordinates enrollment and data collection. Pregnant individuals who are interested in participating in the study answer a set of screening eligibility questions via a web-based application or by calling the VRCC. If eligible, the individual will be asked to provide informed consent, their primary contact information, alternate contact information, contact information for HCPs who are/will be involved in their care or the care of their infant, and medical releases to allow these HCPs to provide data to the registry.
Inclusion criteria for the CorEvitas Inflammatory Bowel Disease Pregnancy Registry (IBD-PR) are as follows:

1. Currently pregnant
2. 15 to 50 years of age at enrollment
3. Diagnosis of an inflammatory bowel disease, including ulcerative colitis (UC), Crohn's disease, other and unspecified noninfective gastroenteritis and colitis (ICD-10 K52), or indeterminate colitis (ICD-10 K52.3)
4. Evidence of a personally signed and dated informed consent document or, upon waiver of written consent by the relevant institutional review board/independent ethics committee, verbal consent, indicating that the individual (or a legally acceptable representative) has been informed of all pertinent aspects of the study
5. Authorization for their HCP(s) to provide data to the registry
6. Contact information is available (for participant and HCPs)

The exclusion criterion for IBD-PR is: exposure to methotrexate during pregnancy

Data Reporters

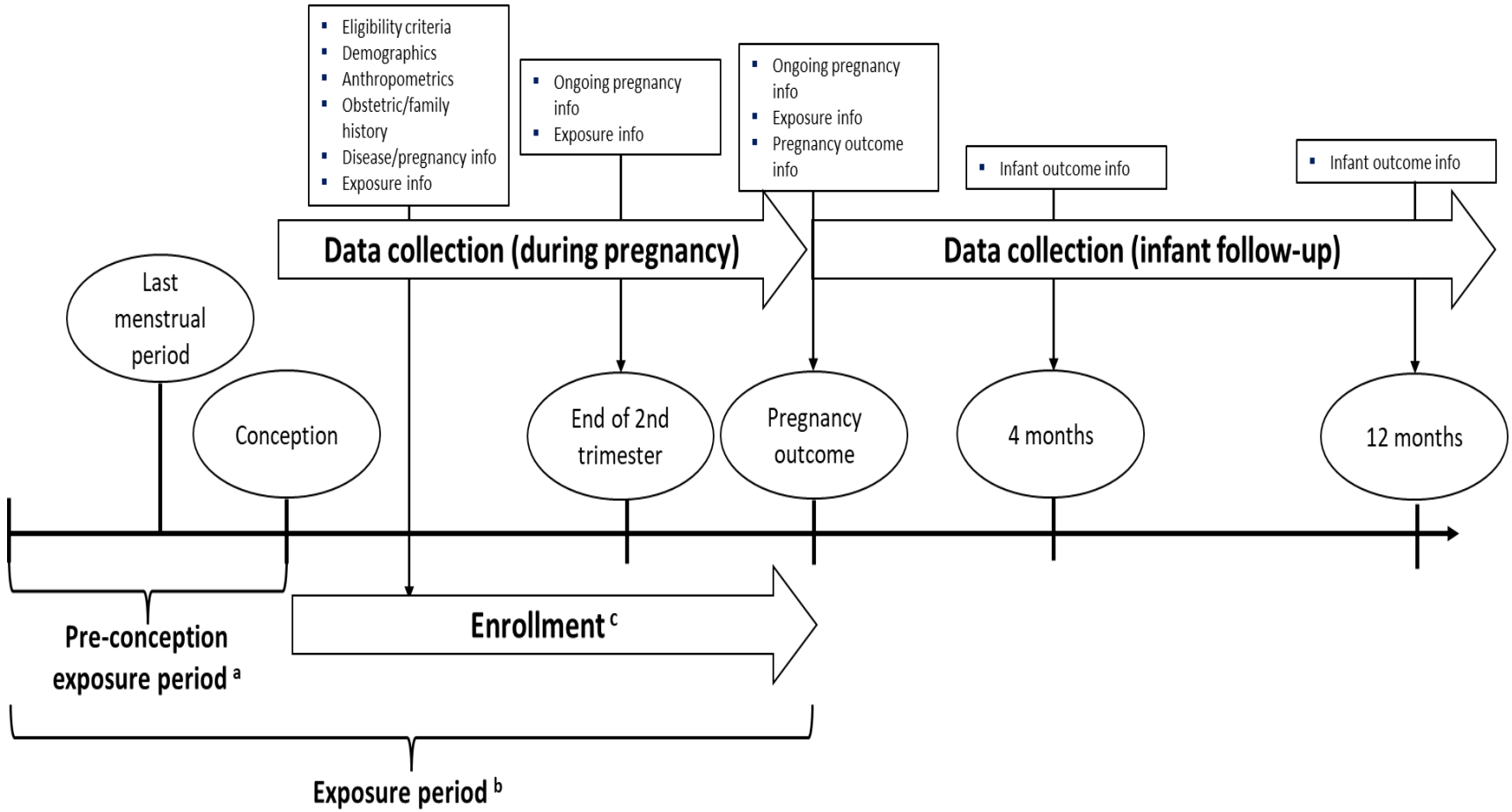
Information on all study variables is collected from enrolled pregnant individuals and the HCPs involved in their care or the care of their infants. As described in Table 5, most obstetric data are collected from the participant's obstetric HCP (e.g., obstetrician, family practitioner, general practitioner who provides care during pregnancy) and most infant data are collected from the infant's pediatric HCP (e.g., pediatrician, family practitioner, general practitioner who provides pediatric care). After enrollment, the registry may also request data from other HCPs involved in the participant's or infant's care (e.g., prescriber, specialist) or from additional HCPs who were not identified at enrollment (e.g., if a participant does not know who their pediatric HCP will be at the time of enrollment or switches HCPs after enrollment) after appropriate medical releases are obtained from the participant.
Reporters use electronic forms or paper data collection forms that can be submitted via email/fax, or via phone interview. HCP reporters are instructed to transcribe data from the participant's or infant's medical records into the data collection forms.
When a data collection form or requested response is not received within 10 days, the IBD-PR Study Team will follow-up via various contact modalities (e-mail, SMS, call), taking into

account any information collected from the participant about their communication preferences for a total of 4 attempts. Initial follow-up contact will be twice in the first week, then once in each of the next 2 weeks. Whenever calls are made in an attempt to contact the participant, an automated email will also be sent explaining an attempt to contact was made and that participant is requested to contact the VRCC by phone or email or to complete the required data collection forms online. Following this, one final attempt to contact the participant will be made, and an email will be sent explaining they will be lost to follow-up and their participation in the registry will end if no response is received. If no response is received, the participant will be considered as lost to follow up within 1 month of the initial follow-up contact.

Data Collection Schedule

All participants are followed through the end of pregnancy and all liveborn infants will be followed through 1 year of age (Figure 1). Information will be collected at enrollment, at the end of the second trimester (approximately 26 gestational weeks), and at the end of pregnancy (live birth or fetal loss). The second pregnancy assessment is scheduled for the end of the second trimester because it is after important diagnostic tests like the 20-week anatomy scan.
Infant data are collected at 4 and 12 months of age. To reduce recall bias, pediatric HCPs are asked to provide data that are routinely documented in the infants' medical records at their visits at 4 and 12 months of age. This schedule follows the American Academy of Pediatrics infant well-child visit schedule (AAP 2022).
Figure 1 and Table 5 provide a summary of the data collection forms and schedule.

Figure 1. Data Collection Schedule



[a] Time to product elimination (5 times terminal half-life); etrasimod half-life = 30 hours ; therefore, time to elimination = 7 days (150 hours)

[b] If a participant is exposed to the product during this time period, she will be considered exposed during pregnancy

[c] Participants may be retrospectively enrolled into the registry up to one year after pregnancy outcome but will not be included in main analysis

Table 5. Summary of Data Collection Forms

Data Collection Form	Reporters	Timing of Completion	Data Collected
Registration Form for Participants	Participant	Enrollment	• Registration information, including eligibility criteria • Maternal demographic characteristics • Maternal pre-pregnancy anthropometrics
Registration Form for HCPs	Obstetric HCP and prescribing HCP, if needed	Enrollment	• Registration information, including eligibility criteria • Maternal obstetrical history • Family history of congenital malformations • UC information • Baseline pregnancy information
Pregnancy Information Form	Obstetric HCP and prescribing HCP, if needed	Enrollment, end of second trimester,[1] and EDD/pregnancy outcome[1]	• Ongoing pregnancy information • Maternal exposures during pregnancy
Maternal Health Form	Obstetric HCP and prescribing HCP, if needed	Enrollment, end of the second trimester (around 26 to $27^{6/7}$ weeks),[1] and EDD/pregnancy outcome[1]	• Medical conditions • Death
Pregnancy Outcome Form	Obstetric HCP and pediatric HCP, if needed	EDD/pregnancy outcome	• Pregnancy outcome information
Infant Outcomes Form	Pediatric HCP	4 and 12 months after delivery	• Infant outcome information at 4 and 12 months
Targeted Follow-up Form	Obstetric, pediatric, or other HCP	Any time after pregnancy outcome	• Targeted follow-up information

EDD = estimated date of delivery; HCP = healthcare provider; UC = ulcerative colitis
1 Obtain updated information since the previous contact.

Data Collected

Maternal Information

- Source of information (e.g., obstetrician, HCP prescriber)
- Birth date
- Country of residence
- Ethnicity (Hispanic or Latino, not Hispanic or Latino)
- Highest level of education

- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or other Pacific Islander, White)
- Employment status
- Household income
- Medical insurance status
- Height
- Obstetrical history:
    - Number of previous pregnancies/fetuses and outcome of each
    - Previous maternal pregnancy complications
    - Previous fetal/live birth abnormalities and type
    - For each previous live birth, gestational age delivered and birth weight
- Family history (specify type, maternal or paternal, among others) of malformations and genetic disorders
- Type if IBD, date of diagnosis, severity of disease, type/location of disease
- History of fertility treatments
- Current pregnancy:
    - Pre-pregnancy weight (derived: body mass index)
    - First pregnancy-related healthcare visit during pregnancy
    - Date of LMP
    - Method of conception
    - Date pregnancy confirmed
    - Estimated date of delivery and method of EDD determination. If EDD determined by ultrasound, timing of ultrasound
    - Prenatal test results (including dates)
    - Obstetric complications (e.g., preeclampsia)
    - Number of fetuses, pregnancy outcome. Complications during pregnancy (including any adverse product reactions) and dates
    - Medicinal exposures i.e., drug or biological product exposures (prescription drugs, over-the-counter products, and dietary supplements): Name, dosage and route, start and end date (derived: duration), Indication
    - Recreational drug use (e.g., tobacco, alcohol, illicit drugs)
    - Maternal medical conditions (e.g., hypertension, diabetes, seizure disorder, autoimmune disease)
    - Maternal death and cause of death

Neonatal Information

- Source of information (e.g., obstetrician, pediatrician)
- Date of receipt of information
- Date of birth or termination
- Gestational age at birth or termination
- Gestational outcome
- Sex
- Obstetric complications (e.g., preeclampsia, premature delivery)
- Pregnancy order (singleton, twin, triplet)
- Results of neonatal physical examination
- Anomalies diagnosed at birth or termination
- Anomalies diagnosed after birth
- Weight at birth indicating whether small, appropriate, or large for gestational age
- Length at birth
- Head circumference at birth indicating whether small, appropriate, or large for gestational age
- Condition at birth (including, when available, Apgar scores at 1 and 5 minutes)
- Developmental assessment
- Infant illnesses, infections (including drug therapies), hospitalizations
- Infant death

ANNEX 2. LIST OF KNOWN TERATOGENS

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

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

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Telmisartan	24 h	6 days prior to DOC	1st, 2nd, and 3rd trimesters
	Valsartan	6 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
Angiotensin-converting enzyme inhibitor	Benazepril	10 to 11 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Captopril	2 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Cilazapril	9 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Enalapril	11 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Fosinopril	11.5 to 14 h	4 days prior to DOC	1st, 2nd, and 3rd trimesters
	Lisinopril	12 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Moexipril	12 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Perindopril	0.8 to 1 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Quinapril	3 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Ramipril	13 to 17 h	4 days prior to DOC	1st, 2nd, and 3rd trimesters
	Trandolapril	6 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
Antiarrhythmic	Amiodarone	61 d	11 months prior to DOC	1st, 2nd, and 3rd trimesters
	Dronedarone	13 to 19 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
Antibiotic	Kanamycin	2 to 3 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Streptomycin	2 to 4.7 h	2 days prior to DOC	1 day prior to DOC, and 1st, 2nd, and 3rd trimesters
	Sulfamethoxazole/ Trimethoprim	8 to 10 h	3 months prior to DOC	3 months prior to conception and 1st trimester for MCMs and 2nd trimester for preterm birth and LBW

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Telavancin	8 h	2 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Demeclocycline	10 to 17 h	4 days prior to DOC	2nd and 3rd trimesters
	Oxytetracycline	6 to 11 h	3 days prior to DOC	2nd and 3rd trimesters
	Tetracycline	6 to 11 h	3 days prior to DOC	2nd and 3rd trimesters; limited data for first trimester exposure
	Chlortetracycline	5.6 h	2 days prior to DOC	Unknown. Assumed window: 2nd and 3rd trimesters
	Doxycycline	18 to 22 h	5 days prior to DOC	Unknown. Assumed window: 2nd and 3rd trimesters
	Methacycline	14 to 22 h	5 days prior to DOC	Unknown. Assumed window: 2nd and 3rd trimesters
	Minocycline	11 to 24.31 h	6 days prior to DOC	Unknown. Assumed window: 2nd and 3rd trimesters
	Tigecycline	27 to 43 h	10 days prior to DOC	Unknown. Assumed window: 2nd and 3rd trimesters
Anticoagulant	Acenocoumarol	8 to 11 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Dicumarol	1 to 2 d	14 days prior to DOC	At least 2 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Phenprocoumon	4 to 6 d	33 days prior to DOC	1st, 2nd, and 3rd trimesters
	Warfarin	40 h	14 days prior to DOC	At least 2 weeks before LMP and 1st, 2nd, and 3rd trimesters
Anticonvulsant	Trimethadione/Paramethadione	Paramethadione: 12 to 24 h Trimethadione: 11 to 16 h	6 days prior to DOC	1st, 2nd, and 3rd trimesters
	Valproic acid / Valproate / Divalproex sodium	9 to 16 h	4 days prior to DOC	Primarily 1st trimester, but MCMs have been

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
				associated with 2nd and 3rd trimester exposures
	Carbamazepine	12 to 65 h	15 days prior to DOC	1st, 2nd, and 3rd trimesters
	Ethotoin	3 to 9 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Phenytoin / Fosphenytoin	Phenytoin: 7 to 42 h Fosphenytoin: 15 min	10 days prior to DOC	1st, 2nd, and 3rd trimesters
	Primidone	10 h	3 days prior to DOC	1st, 2nd, and 3rd trimesters
	Topiramate	21 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Ethosuximide	17 to 56 h	13 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Methsuximide or mesuximide	1.4 to 2.6 h for mesuximide and 2 to 38 h for the active metabolite	9 days prior to DOC	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 DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Sultiame	24 h	6 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Vigabatrin	10.5 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Phenobarbital	70 to 140 h	33 days prior to DOC	1st, 2nd, and 3rd trimesters
	Methylphenobarbital	34 h	8 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
Antidepressant	Brexanolone	9 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Esketamine	12 h	3 days prior to DOC	3 days prior to conception, and 2nd, and 3rd trimesters
	Paroxetine	21 h	5 days prior to DOC	5 days prior to conception, and 1st trimester
Antifungal	Fluconazole	30 h	2 weeks prior to DOC	2 weeks before LMP and 1st trimester
	Flucytosine	2.4 to 4.8 h	2 days prior to DOC	1st trimester
	Posaconazole	35 h (range, 20 to 66 h)	16 days prior to DOC	1st, 2nd, and 3rd trimesters
	Voriconazole	Terminal half-life of elimination is dose-dependent		1st, 2nd, and 3rd trimesters
Antineoplastic	Abemaciclib	18.3 h	3 weeks prior to DOC	3 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Afatinib	37 h	2 weeks prior to DOC	2 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Aminopterin	12 to 24 h	6 days prior to DOC	1st, 2nd, and 3rd trimesters
	Asparaginase	5.7 d	3 months prior to DOC	3 months before LMP and 1st, 2nd, and 3rd trimesters
	Axitinib	2.5 to 6.1 h	1 week prior to DOC	1 week before LMP and 1st, 2nd, and 3rd trimesters
	Azacitidine	4 h for IV and SC administrations	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Bosutinib	22.5 (SD, 1.7)	2 weeks prior to DOC	2 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Brentuximab vedotin	4 to 6 d	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Methotrexate	55 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Cabozantinib	99 h	4 months prior to DOC	4 months before LMP and 1st, 2nd, and 3rd trimesters
	Ceritinib	41 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Crizotinib	42 h	45 days prior to DOC	45 days before LMP and 1st, 2nd, and 3rd trimesters
	Cytarabine	1 to 3 h	6 months prior to DOC	6 months before LMP 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 DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Decitabine	0.54 h to 0.62 h depending on administration schedules	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Exemestane	24 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Mechlorethamine	15 min	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Mercaptopurine	10 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Mitotane	18 to 159 days (median, 53 days)	30 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Pazopanib	31 h	2 weeks prior to DOC	2 weeks before LMP and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Pertuzumab	18 days (median)	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Ponatinib	24 h (12 to 66 h), mean (range)	3 weeks prior to DOC	3 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Pralatrexate	12 to 18 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Ramucirumab	14 days (mean)	3 months prior to DOC	3 months before LMP and 1st, 2nd, and 3rd trimesters
	Regorafenib	51 h (32 to 70 h), mean (range)	2 months prior to DOC	2 months before LMP and 1st, 2nd, and 3rd trimesters
	Romidepsin	3 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Ruxolitinib	3 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Selumetinib	6.2 h	1 week prior to DOC	1 week before LMP and 1st, 2nd, and 3rd trimesters
	Talimogene laherparepvec	Not available, although it has been found in patients' injected tumors through 84 days	16 months prior to DOC	1st, 2nd, and 3rd trimesters
	Tivozanib	111 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Tofacitinib	3 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Trabectedin	175 h	2 months prior to DOC	2 months before LMP and 1st, 2nd, and 3rd trimesters
	Trametinib	3.9 to 4.8 days	4 months prior to DOC	4 months before LMP and 1st, 2nd, and 3rd trimesters
	Trastuzumab	28 days	7 months prior to DOC	7 months before LMP and 1st, 2nd, and 3rd trimesters
	Tucatinib	11.9 h	1 week prior to DOC	1 week before LMP and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Vandetanib	19 days (median)	4 months prior to DOC	4 months before LMP and 1st, 2nd, and 3rd trimesters
	Vemurafenib	57 h (median)	2 weeks prior to DOC	2 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Vinblastine	24.8 h	6 days prior to DOC	1st, 2nd, and 3rd trimesters
	Vismodegib	4 days after continuous once-daily dosing 12 days after a single dose	7 months prior to DOC	7 months before LMP and 1st, 2nd, and 3rd trimesters
	Vorinostat	2 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Zanubrutinib	2 to 4 h	1 day prior to DOC	1 week before LMP and 1st, 2nd, and 3rd trimesters
	Cyclophosphamide	3 to 12 h	12 months prior to DOC	12 months before LMP and 1st trimester
	Altretamine	4.7 to 10.2 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Amsacrine	8 to 9 h	3 months prior to DOC	3 months before LMP and 1st, 2nd, and 3rd trimesters
	Bevacizumab	480 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Bleomycin	2 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bortezomib	40 to 193 h	7 months prior to DOC	7 months before LMP and 1st, 2nd, and 3rd trimesters
	Busulfan	2.3 to 3.4 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Capecitabine	0.75 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Carboplatin	2.6 to 5.9 h	2 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Carmustine	IV, 15 to 75 min	3 months prior to DOC	3 months before LMP and 1st, 2nd, and 3rd trimesters
	Cetuximab	63 to 230 h	2 months prior to DOC	2 months before LMP and 1st, 2nd, and 3rd trimesters
	Chlorambucil	1.5 h	1 day prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Cisplatin	20 to 30 min	12 months prior to DOC	12 months before LMP and 1st, 2nd, and 3rd trimesters
	Cladribine	1 d	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Clofarabine	5.2 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Dacarbazine	5 h	2 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Dactinomycin	36 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Dasatinib	3 to 5 h	2 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Docetaxel	11.1 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Doxorubicin	20 to 48 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Epirubicin	31.1 h ± 6 h to 35.3 h ± 9 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Erlotinib	36.2 h	2 weeks prior to DOC	2 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Estramustine	10 to 20 h	5 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Etoposide	4 to 11 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Fludarabine	20 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Fluorouracil	8 to 20 min	3 months prior to DOC	3 months before LMP and 1st, 2nd, and 3rd trimesters
	Gemcitabine	1.7 to 19.4 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Hydroxycarbamide	2 to 4.5 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Idarubicin	20 to 22 h	6.5 months prior to DOC	6.5 months before LMP and 1st, 2nd, and 3rd trimesters
	Ifosfamide	15 h	4 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Imatinib	18 h	2 weeks prior to DOC	2 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Irinotecan	6 to 12 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Lapatinib	24 h	1 week prior to DOC	1 week before LMP and 1st, 2nd, and 3rd trimesters
	Lomustine	16 to 48 h	2 weeks prior to DOC	2 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Melphalan	10 to 75 min	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Mitomycin	46 min	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Mitoxantrone	23 to 215 h	50 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Nelarabine	Adults: prodrug: 30 min; ara-G: 3 h	1 day prior to DOC	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 DOC	9 months before LMP and 1st, 2nd, and 3rd trimesters
	Paclitaxel	13 to 52 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Pemetrexed	3.5 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Pembrolizumab	22 d	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Pentostatin	5.7 h	2 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Azacytidine	4 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Bendamustine hydrochloride	Intermediate: 40 mins Terminal: 3 h 30 mins	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Brequinar	8 h	2 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Cabazitaxel	95 h	22 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Dabrafenib	8 h	2 weeks prior to DOC	2 weeks before LMP and 1st, 2nd, and 3rd trimesters
	Eribulin	40 h	10 days prior to DOC	1st, 2nd, and 3rd trimesters
	Everolimus	30 h	7 days prior to DOC	7 days prior to conception, and 1st trimester, 2nd, and 3rd trimesters
	Floxuridine	Not available	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Gefitinib	48 h	11 days prior to DOC	1st, 2nd, and 3rd trimesters
	Hydroxyurea	2 to 3 h in adults	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Ixabepilone	52 h	7 months prior to DOC	7 months before LMP and 1st, 2nd, and 3rd trimesters
	Lenvatinib	28 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Trimetrexate glucuronate	7 to 15 h	4 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Procarbazine	(IV), approximately 10 min	1 day prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Raltitrexed	260 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Sorafenib	25 to 48 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Streptozocin	Systemic: 35 min unchanged drug; 40 h metabolites	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Sunitinib	40 to 60 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Tegafur	6.7 to 11.3 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Temozolomide	1.8 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Teniposide	5 h	2 days prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Thioguanine	80 min	1 day prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Thiotepa	1.4 to 3.7 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Topotecan	2 to 3 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Vincristine	85 h	20 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Vindesine	2.9 h	1 day prior to DOC	Not in TERIS. Assumed window: 1st, 2nd, and 3rd trimesters
	Vinorelbine	27.7 to 43.6 h	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
	Lenalidomide	3 h	4 weeks prior to DOC	4 weeks before LMP and 1st, 2nd, and 3rd trimesters
Antithyroid	Propylthiouracil	1 to 2 h	1 day prior to DOC	1st and 2nd trimesters
	Methimazole (Carbimazole)	4.9 to 5.7 h	2 days prior to DOC	1st, 2nd, and 3rd trimesters
	I-131 (radioiodine)	192 h	12 months prior to DOC	6 to 12 months before LMP and 1st, 2nd, and 3rd trimesters
Antiviral	Ribavirin	12 d	6 months prior to DOC	6 months before LMP and 1st, 2nd, and 3rd trimesters
Endothelin receptor antagonist	Ambrisentan	15 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Bosentan	5 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Macitentan	16 to 48 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
Estrogen	Diethylstilbestrol	Diethylstilbestrol reaches peak concentration within 20 to 40 min, having a primary half-life of 3 to 6 h. It has a terminal half-life of 2 to 3 d due to entero-hepatic circulation	17 days prior to DOC	1st, 2nd, and 3rd trimesters
	Mycophenolate mofetil	16 h	4 days prior to DOC	1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
Immuno-modulatory agent	Thalidomide	5 to 7 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Penicillamine	2 to 4 h	1 day prior to DOC	1st, 2nd, and 3rd trimesters
	Azathioprine	5 h	2 days prior to DOC	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Leflunomide	432 to 456 h	2 years prior to DOC	2 years before LMP and 1st, 2nd, and 3rd trimesters
	Mycophenolic acid	8 to 16 h	4 days prior to DOC	Primarily 1st trimester, but other outcomes have been associated with exposures "during pregnancy"
	Pomalidomide	9.5 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Teriflunomide	19 days	105 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
Mood stabilizer	Lithium	24 h	6 days prior to DOC	1st, 2nd, and 3rd trimesters
Nonsteroidal anti-inflammatory drug	Aspirin	30 h	7 days prior to DOC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exposure
	Ibuprofen	2.2 h	1 day prior to DOC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exposure
	Indomethacin	4.5 h	1 day prior to DOC	2nd and 3rd trimesters; unlikely risk associated with 1st trimester exposure
	Naproxen	17 h	4 days prior to DOC	2nd and 3rd trimesters; unlikely risk associated with

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
				1st trimester exposure
Prostaglandins analogue	Misoprostol	20 to 40 min	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
Retinoid	Alitretinoin	9 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Tretinoin	0.5 to 2 h	1 day prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	High dose vitamin A (>10,000 IU/day)	TERIS only notes "long half-life"	14 months prior to DOC	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	3 years prior to DOC	3 years before LMP and throughout pregnancy, especially 1st trimester
	Bexarotene	7 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Etretinate	120 d	3 years prior to DOC	3 years before LMP and throughout pregnancy, especially 1st trimester
	Isotretinoin	10 to 12 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Tazarotene	18 h	5 days prior to DOC	1st, 2nd, and 3rd trimesters
	Retinol	2 to 9 h	12 months prior to DOC	12 months before LMP and 1st trimester
Steroid	Danazol	9.7 to 23.7 h	6 days prior to DOC	1st, 2nd, and 3rd trimesters
Tyrosine kinase inhibitor	Aflibercept	120 to 144 h	33 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Axitinib	2.5 to 6.1 h	1 week prior to DOC	1 week before LMP and 1st, 2nd, and 3rd trimesters

Drug Class	Generic Name	Half Life	Pre-Conception Exposure Window[1]	Relevant Exposure Window
	Ibrutinib	4 to 6 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Lestaurtinib	NA	NA	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Nilotinib	17 h	4 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters
	Nintedanib	10 to 15 h	3 months prior to DOC	3 months before LMP and 1st, 2nd, and 3rd trimesters
Other	Methylene blue	24 h	6 days prior to DOC	6 days prior to conception, and 1st, 2nd, and 3rd trimesters
	Riociguat	7 to 12 h	1 month prior to DOC	1 month before LMP and 1st, 2nd, and 3rd trimesters
	Sparsentan	9.6 h	3 days prior to DOC	Unknown. Assumed window: 1st, 2nd, and 3rd trimesters

ara-G = guanine nucleoside analogue; ARB = angiotensin receptor blocker; DOC = date of conception; IV = intravenous; LBW = low birth weight; LMP = last menstrual period; MCM = major congenital malformation; N/A = not applicable; SC = subcutaneous; TERIS = Teratogen Information System.
1 A pregnant patient will be considered exposed during the 1st trimester if a dose is taken during this preconception exposure window. The exposure window was calculated based on either 5.5 half-lives of the product or based on information from the literature, whichever is longer.
Sources: Eltonsy 2016; TERIS 2021; DrugBank online available at https://go.drugbank.com; product labels, which are available at: https://www.accessdata.fda.gov/scripts/cder/daf/ and https://dailymed.nlm.nih.gov/dailymed/index.cfm; summary of product characteristics at https://www.ema.europa.eu/en/medicines and https://products.mhra.gov.uk/, product monographs at https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html.

ADDITIONAL INFORMATION

Not applicable.

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