Protocol I6T-MC-B003
Observational Study of Pregnancy and Infant Outcomes Among Women Exposed to Mirikizumab During Pregnancy in US-based Administrative Claims Data

Document ID: VV-PVG-109147

Post-Authorisation Safety Study (PASS) Information

Title	Observational Study of Pregnancy and Infant Outcomes Among Women Exposed to Mirikizumab During Pregnancy in US-based Administrative Claims Data
Study Identifier	I6T-MC-B003
Version Identifier	V1
Date of Last Version	N/A
EU PAS Register No:	EUPAS105674
Active Substance	Immunosuppressants, interleukin inhibitors, ATC code: L04AC24
Medicinal Product(s)	Omvoh™ (active substance: mirikizumab)
Product Reference	Marketing Authorisation Numbers: EU/1/23/1736/001 to 006
Procedure Number	EMEA/H/C/005122/0000
Marketing Authorisation Holder(s)	Eli Lilly Nederland B.V.
Joint PASS	No
Research Question and Objectives	The overall aim of this study is to evaluate the safety of mirikizumab in pregnant women and their infants. To achieve this aim, there are 3 objectives: Objective 1: To monitor the use of mirikizumab during pregnancy by describing the demographic and clinical characteristics of women who are exposed to mirikizumab during pregnancy. Objective 2: To describe the occurrence of adverse pregnancy and infant outcomes of interest among women with ulcerative colitis (UC) (and infants linked to these women) who are exposed during pregnancy to: ● Mirikizumab ● Anti-tumour necrosis factors (aTNFs) ● Vedolizumab ● Ustekinumab The adverse pregnancy and infant outcomes of interest include: ● Primary outcome: major congenital malformations (MCM) ● Secondary outcomes: spontaneous abortions (SA), stillbirth (SB), preterm birth (PTB), small for gestational age (SGA) Objective 3: To compare the relative risk (risk ratio) of the adverse pregnancy and infant outcomes of interest among women with UC (and infants linked to these women) who are exposed to mirikizumab during pregnancy, compared to the following comparator groups of women with UC (and infants linked to these women) who are exposed during pregnancy to: 1) aTNFs, 2) vedolizumab, 3) ustekinumab for UC. This objective will only be analysed if sufficient sample sizes of mirikizumab and comparator group exposed pregnancies for the pregnancy outcomes (SA, SB, PTB), and a sufficient number of exposed pregnancies with linked infants for the infant outcomes (MCM, SGA) are attained.
Country(ies) of study	United States
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Marketing Authorisation Holder

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2. List of Abbreviations

Term	Definition
5-ASA	5-aminosalicyclic-acid
ASD	absolute standardised difference
ATC	Anatomical Therapeutic Chemical Classification System
ATE	average treatment effect
aTNF	anti-tumour necrosis factor
AE	adverse event
AEP	Aetion Evidence Platform®
BMI	body mass index
CD	Crohn's Disease
CD28	cluster of differentiation 28
CI	confidence interval
CPT	Current Procedural Terminology
DRG	diagnosis-related group
DNA	deoxyribonucleic acid
EHR	electronic health record
EMA/EMEA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
ERB	ethical review board
EU	European Union
EU PAS	European Union post-authorisation study
EUROCAT	European Registration of Congenital Anomalies and Twins

Term	Definition
FDA	Food and Drug Administration
GA	gestational age
GEP	Good Epidemiologic Practice
GPP	Good Pharmacoepidemiologic Practice
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
IBD	inflammatory bowel disease
ICD-10-CM	International Classification of Diseases, Tenth Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, Tenth Revision, Procedure Coding System
IL	interleukin
IPTW	inverse probability of treatment weighting
ISPE	International Society for Pharmaceutical Engineering
ITT	intention-to-treat
IV	intravenous
IQR	interquartile range
JAKi	Janus kinase inhibitor
LB	live birth
LBW	low birth weight
LMP	last menstrual period
MAH	Marketing Authorisation Holder
MCM	major congenital malformation
MOM	HealthVerity Maternal Outcomes Masterset

Term	Definition
MTX	methotrexate
NDC	National Drug Code
NSAID	nonsteroidal anti-inflammatory drug
OTC	over-the-counter
PASS	post-authorisation safety study
PHI	protected health information
PII	personal identifying information
PPV	positive predictive value
PS	propensity score
PTB	preterm birth
RA	rheumatoid arthritis
RCT	randomised controlled clinical trial
SA	spontaneous abortion
SAP	statistical analysis plan
SB	stillbirth
SC	subcutaneous
SD	standard deviation
SGA	small for gestational age
TTE	target-trial emulation
UC	ulcerative colitis
US	United States

3. Responsible Parties

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4. Abstract

- **Title:** Observational Study of Pregnancy and Infant Outcomes Among Women Exposed to Mirikizumab During Pregnancy in US-based Administrative Claims Data
- **Rationale and background:** Ulcerative Colitis (UC) is a chronic immune-mediated disorder that is characterised by inflammation and ulceration of the colonic mucosa. There are no curative therapies for UC; rather, the goal of medical therapy is to achieve steroid-free clinical and endoscopic remission with the intention of preventing severe complications and invasive surgery. Mirikizumab is a humanised, immunoglobulin G4 monoclonal antibody that specifically targets the p19 subunit of IL-23 and is approved by the US FDA for the treatment of moderately to severely active UC in adults, and by the European Commission for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment. Given the long-term treatment, age distribution, and high risk of pregnancy complications in patients with UC, the safety of mirikizumab in pregnancy is a particularly relevant question for this patient population. The protocol herein describes an observational study to assess pregnancy and infant outcomes following exposure to mirikizumab in pregnancy in US-based administrative claims data.
- **Research question and objectives:** The overall aim of this study is to evaluate the safety of mirikizumab in pregnant women and their infants. To achieve this aim, there are 3 objectives:

  Objective 1: To monitor the use of mirikizumab during pregnancy by describing the demographic and clinical characteristics of women who are exposed to mirikizumab during pregnancy.

  Objective 2: To describe the occurrence of adverse pregnancy and infant outcomes of interest among women with UC (and infants linked to these women) who are exposed during pregnancy to:

  - mirikizumab
  - anti-tumour necrosis factor drugs (aTNFs) - adalimumab, golimumab, and infliximab
  - α4β7 integrin inhibitor – vedolizumab, or
  - interleukin (IL) 12/23 inhibitor - ustekinumab

  The adverse pregnancy and infant outcomes of interest include:

  - primary outcome: major congenital malformations (MCMs) and
  - secondary outcomes: spontaneous abortion (SA), stillbirth (SB), preterm birth (PTB), small for gestational age (SGA).

  Objective 3: To compare the relative risk (risk ratio) of adverse pregnancy and infant outcomes of interest among women with UC (and infants linked to these women) who are exposed to mirikizumab during pregnancy, compared to the following comparator groups of women with UC (and infants linked to these women) who are exposed during pregnancy to: 1) aTNFs, 2) vedolizumab, or 3) ustekinumab.

This objective will only be analysed if sufficient sample sizes of mirikizumab and comparator group exposed pregnancies for the pregnancy outcomes (SA, SB, PTB), and a sufficient number of exposed pregnancies with linked infants for the infant outcomes (MCM, SGA) are attained.

- **Study design:** This is a secondary database cohort study leveraging US administrative insurance claims data where capabilities exist to link mothers and offspring within the claims records.
- **Population:** The source population for this study consists of patients in the HealthVerity Maternal Outcomes Masterset (MOM) database which contains information on pregnancies starting from 01 January 2018 and historical pharmacy and medical claims information on these pregnant women starting 01 January 2008 (start of available data in the study database).

  The pregnancy identification period starts on 26 October 2023 (the date of mirikizumab approval in the US) through 31 December 2030 (one year prior to delivery of final study report). Individuals with evidence of a pregnancy will be identified and pregnancy episodes will be created using a validated algorithm (Moll et al. 2021). This algorithm identifies pregnancy start dates and end dates by estimating the first day of the last menstrual period (LMP) and from that point, estimates of gestational age (GA) at various time points during the pregnancy episode are assigned.

  There will be five study cohorts in this study.

  The first study cohort will be women with evidence of exposure to mirikizumab during pregnancy, regardless of the history of UC (Objective 1).
    - Within this cohort, a nested cohort of women with a diagnosis of UC will be generated for descriptive (Objective 2) and comparative analysis (Objective 3) purposes.

  Three separate comparator cohorts will be considered (Objectives 2 and 3), and will include women with UC that:

    - were exposed to aTNF during the pregnancy episode(s) of interest,
    - were exposed to vedolizumab during the pregnancy episode(s) of interest, or
    - were exposed to ustekinumab during the pregnancy episode(s) of interest

  For cohort classification for Objectives 2 and 3, mirikizumab or comparator exposure cohort assignment will be based on the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after the LMP but within the relevant outcome specific exposure assessment window (defined under Study Period below in the abstract and in Section 9.2.2). When the first qualifying medication exposure occurs during the 5 half-lives before LMP or on the LMP date, the start of follow-up begins at LMP. When the first qualifying medication exposure occurs after the LMP date, the start of follow-up begins on the date of the first qualifying exposure. Women who are exposed to multiple UC biologic medications on the start of follow up will be excluded.

- **Variables:**
    - **Exposures:** Exposure to mirikizumab or a comparator medication during the pregnancy episode will be assessed based on information recorded in the prescription and medical claims (e.g., prescription claims date, days' supply, date of medication administration).

      A woman will be considered exposed during the pregnancy episode (defined as the first day of LMP up until end of pregnancy) and assigned to mirikizumab or comparator cohorts if they are exposed to either mirikizumab or comparator medication during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome-specific exposure assessment window (defined under Study Period below in the abstract and in Section 9.2.2).

      Women who are exposed to multiple UC biologic medications on the start of follow up will be excluded. Therefore, women cannot qualify for more than one cohort. However, during the qualifying pregnancy episode, women who switch medication or are exposed to a JAKi after cohort entry, will be retained in the original cohort (i.e., TTE observational analogue of an ITT approach).

      Pregnant women may have concomitant exposure to non-biologic medications that are indicated for treatment of UC, such as aminosalicylates (e.g., azathioprine) during the qualifying pregnancy episode (see Section 9.3.1 for a list of relevant non-biologic treatments).

    - Due to the length of the study period, it is possible that some women may contribute multiple pregnancy episodes to these analyses.

    - Covariates: Relevant variables will be collected for descriptive purposes and as a means for balancing cohorts in comparative analyses if a sufficient sample size is achieved. Variables assessed prior to the start of follow-up (defined further below in the abstract) will be considered for inclusion in propensity score (PS) models, and include maternal demographics, clinical characteristics, pregnancy and obstetric history, comorbid conditions (e.g., diabetes, hypertension, obesity), time to first qualifying exposure after the LMP date, and others. Variables that are assessed following the first qualifying cohort exposure during the pregnancy episode, including exposure to other UC-related treatments, obstetrical conditions, healthcare utilisation during pregnancy, UC subtype, and calendar time on the day of exposure to mirikizumab or comparator treatments will be reported descriptively, only.

- **Outcomes:** The primary outcome of interest is MCM. Secondary outcomes include the pregnancy outcomes of SA, SB, PTB as well as the infant outcome of SGA. Each outcome will be assessed separately during predefined clinically relevant assessment periods (see Section 9.2.1). For example, SB will be defined as involuntary foetal loss at 20 weeks of gestation or after, meaning the clinically relevant assessment window occurs at 20 weeks of gestation or after. Additionally, each outcome will be assessed among the relevant pregnancies with respect to outcome-specific inclusion and exclusion criteria (e.g., mother-infant linkage).

- **Study Period:**
  - **Exposure assessment windows:** The time window in which the exposure is assessed varies by outcome as follows and additional details regarding the exposure assessment is described in Section 9.2.2, Table 9.6 and Annex 1:
    - For MCM outcomes, the exposure assessment period is from 5 half-lives prior to LMP until the end of the first trimester.
    - For SA outcomes, the exposure assessment period is from 5 half-lives prior to LMP until <20 weeks (i.e., 19 weeks and 6 days) of gestation
    - For PTB, the exposure assessment period is from 5 half-lives prior to LMP until <37 weeks (i.e., 36 weeks and 6 days) of gestation
    - For SGA and SB, the exposure assessment period is from 5 half-lives prior to LMP until the end of the pregnancy
  - **Exposure to teratogens:** Exposure to teratogenic medications will be assessed based on pharmacy and/or medical claims for the respective medication for both the mirikizumab UC cohort as well as all UC comparator cohorts. Exposure to teratogens will be considered as use within 5 half-lives of the respective medication prior to the LMP or anytime from the LMP until the first qualifying exposure to mirikizumab or a comparator medication. Examples of potential teratogens and their respective half-lives are described in Appendix D, the full list of relevant teratogens will be provided in the statistical analysis plan.
  - **Pregnancy outcome follow-up periods**:
    - Start of follow up: For the analysis of all study outcomes, if the first qualifying medication exposure occurs on the LMP date or during the 5 half-lives before the LMP date, the start of follow-up will begin on the LMP date. If the first qualifying medication exposure occurs after the LMP date, the start of follow-up will begin on the date of the first qualifying exposure.
    - Outcome assessment windows:
      - For the analysis of SB, if the first qualifying exposure occurs on the LMP date, during the 5 half-lives prior to LMP date, or after the LMP date but before 20 weeks' gestation, then the outcome assessment window will begin at 20 weeks' gestation and end at the occurrence of a SB or end of the pregnancy episode, whichever occurs first. If the first qualifying exposure occurs on or after 20

weeks' gestation, then the outcome assessment window will begin on the date of first qualifying exposure and end at the occurrence of a SB or end of the pregnancy episode, whichever occurs first.

- For the analysis of SA, if the first qualifying exposure occurs on the LMP date or during the 5 half-lives before the LMP date, the outcome assessment window will begin at the LMP date and end at the occurrence of a SA, 20 weeks' gestation or end of the pregnancy episode, whichever occurs first. If the first qualifying exposure occurs after the LMP date and before 20 weeks' gestation, the outcome assessment window will begin on the date of first qualifying exposure and end at the occurrence of a SA, 20 weeks' gestation, or end of the pregnancy episode, whichever occurs first.

- For the analysis of PTB, if the first qualifying exposure occurs on the LMP date, during the 5 half-lives before the LMP date, or after the LMP date but before 22 weeks' gestation, the outcome assessment window will begin at 22 weeks' gestation and end at the occurrence of PTB, 37 weeks' gestation or the end of the pregnancy episode, whichever occurs first. If the first qualifying exposure occurs after the LMP date and on or after 22 weeks' gestation but before 37 weeks' gestation, the outcome assessment window begins on the date of first qualifying exposure and ends at the occurrence of PTB, 37 weeks' gestation or the end of the pregnancy episode, whichever occurs first.

- Infant outcome f**ollow-up periods:** The MCM and SGA outcomes will both be assessed during the follow-up period using infant claims data. For all infant outcomes, the outcome must occur after the first qualifying exposure.

  - The MCM outcome will be evaluated two different ways: as a composite outcome (presence of at least one MCM) and by organ class (presence of at least one MCM within that specified organ class). For the composite MCM outcomes, MCMs will be assessed in the 365 days after birth (to allow for sufficient opportunity for MCM to be diagnosed and recorded in the claims data). Infants will be followed from birth until the occurrence of either an MCM diagnosis, 365 days of follow-up, infant disenrollment (allowing ≤30 day enrolment gaps), infant death, or end of the study period, whichever occurs first. More details pertaining to the analysis of MCMs by organ class can be found in Section 9.2.2.

  - SGA will be assessed in the 30 days after birth (to allow for sufficient opportunity for SGA to be diagnosed and recorded in the claims data). Infants will be followed from birth until the occurrence of either SGA outcome, 30 days of follow-up, infant disenrollment, infant death, or end of study period, whichever occurs first.

- **Data sources:** All analyses will use patient-level claims data using the HealthVerity MOM, a large, national, closed claims dataset that contains information regarding pregnant women and their infants. The entire MOM dataset contains information on nearly 2 million pregnant women (HealthVerity 2023). A subset of the pregnancies with live births have linked infant records. If there is sufficient sample size of mirikizumab and comparator group exposed pregnancies for pregnancy outcomes, and sufficient number of women with linked infants for infant outcomes, this data can provide the opportunity to evaluate the impact of maternal exposure during pregnancy on infant outcomes in this linked subgroup.
- **Study size:** The required sample size is calculated for the primary outcome of any MCM among liveborns. Sample size calculations assume a prevalence of 3% in all comparator groups; this is consistent with background risks in the general population (CDC 2008; Clowse et al. 2016; Mahadevan et al. 2018). The sample size was calculated to detect a minimum relative risk of at least 2.5, with a 2-sided probability of type 1 error (alpha) of 5%, and 80% power. With these assumptions, 368 mirikizumab-exposed mother-infant linked pregnancy episodes and 368 mother-infant linked pregnancy episodes in each of the comparator groups of interest will be targeted for the MCM composite outcome.
- **Data analysis:** The purpose of Objective 1 is to describe demographic and clinical characteristics of all pregnancies with evidence of exposure to mirikizumab, irrespective of UC diagnosis or infant linkage. Dichotomous and categorical variables will be summarised using counts with percentages, and non-missing values of continuous variables will be summarised using means with standard deviations (SD) and medians with interquartile range (IQR).

  The purpose of Objective 2 is to summarise the occurrence of the prespecified pregnancy outcomes (SA, SB, PTB) and infant outcomes (MCM with first trimester exposure, SGA) among infants linked to mothers with UC with evidence of exposure to mirikizumab, aTNFs, vedolizumab, or ustekinumab during pregnancy, separately. Counts of outcomes will be presented, along with estimated timing of exposure by trimester to mirikizumab or comparator group treatments for those with the event. The prevalence of each outcome will be reported as count per 100 pregnancies or live births along with the 95% confidence intervals (CI). Additionally, incidence rates will be reported for the MCM outcome as count per 1000 person-years with 95% CIs calculated as number of infants with MCM event / total days in infant outcome follow-up assessment period) / 365 * 1000.

  The purpose of Objective 3 is to compare the relative risk of pregnancy and infant outcomes among pregnancies in women with UC with evidence of mirikizumab exposure versus pregnancies in each of the comparator groups. Objective 3 will be analysed if there is sufficient sample size of mirikizumab and comparator group exposed pregnancies for pregnancy outcomes, and sufficient number of women with linked infants for infant outcomes. Crude and propensity score-adjusted relative risks (95% CI) will be estimated by robust (modified) Poisson regression using a log link and a Poisson distribution without an offset parameter (Zou 2004). Several sensitivity analyses will be conducted to test robustness of results to study specifications.

- **Milestones:** Study progress reports will be provided with the annual Period Safety Update Reports and an Interim report will be submitted to the European Medicines Agency (EMA) approximately 4 years after the start of data collection. Final study report will be submitted to the EMA and the FDA by 31 December 2031.

5. Amendments and Updates

Not applicable.

6. Milestones

Milestones	Anticipated due date
Registration in EU PAS Register	02 October 2023
Draft protocol submission	
EMA	26 November 2023
FDA	30 June 2024
Final protocol submission	
EMA	26 May 2024
FDA	31 December 2024
Start of data collection	Within 2 years of first regulatory approval
Study progress reports	To be provided with the PSUR[a]
Interim report	
EMA	Approximately 4 years after the start of data collection
Study completion	
FDA	31 December 2030
Final study report	
EMA	31 December 2031
FDA	31 December 2031

Abbreviations: EMA = European Medicines Agency; FDA = Food and Drug Administration; PSUR = Periodic Safety Update Report.

[a] After the start of data collection.

7. Rationale and Background

UC is a chronic immune-mediated disorder that is characterised by inflammation and ulceration of the colonic mucosa. It is a relapsing and remitting condition, leading to a significant morbidity and decreased quality of life for affected individuals. The exact aetiology of UC remains unclear; however, it is believed to result from a complex interplay between genetic, environmental, and immunologic factors (Roberts-Thomson et al. 2019).

UC is a form of IBD which often requires long-term pharmacological treatment. While UC can develop at any age, the majority of patients are diagnosed between the ages 30-40 years old (da Silva et al. 2014). Given that UC affects women of reproductive age, special consideration should be given to the implications of its management during pregnancy. Women with IBD have been found to have a higher risk of pregnancy complications including preterm deliveries, SGA, LBW, SA, and congenital abnormalities compared to the general population (Cornish et al. 2007; Bengtson et al. 2010; Oron et al. 2012; Bortoli et al. 2007). Additionally, studies investigating disease activity during pregnancy found that active disease and disease severity were associated with worse birth outcomes including increased risk for SB and SGA in IBD patients (Mahadevan et al. 2007; Oron et al. 2012; Bröms et al. 2014).

There are no curative therapies for UC; rather, the goal of medical therapy is to achieve steroid-free clinical and endoscopic remission with the intention of preventing severe complications and invasive surgery. Until the late 1990s, medication options were limited to thiopurines and MTX, natalizumab, and aTNF. As research continues, new cellular targets in the inflammatory pathway have also been identified (i.e., integrins, IL-12, IL-13, CD28) leading to the widespread use of biologics such as adalimumab (2012), vedolizumab (2014), and ustekinumab (2016) in UC patients (Rawla et al. 2018). Currently, commonly used therapies include non-biologics such as aminosalicylates (e.g., sulfasalazine) and immunomodulators (e.g., azathioprine), biologics such as infliximab, adalimumab, vedolizumab and ustekinumab, and JAKi such as tofacitinib (Feuerstein et al. 2020). JAKi use is contraindicated in pregnancy, as animal studies have demonstrated harmful foetal effects. However, little data is available on the safety of other treatments during pregnancy (Akiyama et al. 2023).

Mirikizumab is a humanised, immunoglobulin G4 monoclonal antibody that specifically targets the p19 subunit of IL-23 and is approved by the US FDA for the treatment of moderately to severely active UC in adults and by the European Commission for the treatment of adult patients with moderately to severely active UC who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment. (D'Haens et al. 2023). Given the long-term treatment, age distribution of UC, and high risk of pregnancy complications in the UC patient population, the safety of mirikizumab in pregnancy is a particularly relevant question. Pregnant women were not included in the mirikizumab clinical development program or were discontinued from the trials if they inadvertently became pregnant during the course of the study. The results from animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity. Further, no reproductive organ weight or histopathology effects were observed in cynomolgus monkeys that received mirikizumab for 26 weeks (EMA 2023). Therefore, data from human studies on the safety of mirikizumab in pregnancy is limited, and its effects on pregnancy and/or foetal and infant outcomes in humans have not been fully determined. As the disease affects women of childbearing age, it is expected

that real-world prescribing of mirikizumab occurs in this population and that pregnancy exposure could occur.

The protocol herein describes an observational study to assess pregnancy and infant outcomes following exposure to mirikizumab in pregnancy in US-based administrative claims data.

In the interest of continued pharmacovigilance and describing use of mirikizumab among pregnant women, this study details two descriptive objectives that will: 1) monitor the use of mirikizumab among all pregnancies, irrespective of whether or not the woman has a UC diagnosis in her claims record or can be linked to an infant; and 2) describe the occurrence of pregnancy and infant outcomes among pregnancies in women with a UC diagnosis who are exposed to mirikizumab during pregnancy. A third, comparative objective will be limited to pregnancies among women with UC. The relative risk of pregnancy and infant outcomes among pregnancies in women with UC treated with mirikizumab versus pregnancies among women with UC in the comparator groups will be calculated. A sufficient sample size of exposed pregnancies and their linked infants will be needed to conduct this analysis. Mirikizumab is indicated for the treatment of moderately to severely active UC. The comparator treatments of interest in the TNFi class, vedolizumab, and ustekinumab are indicated for moderately to severely active UC (Humira package insert, 2018; Remicade package insert, 2011; Simponi package insert, 2019; Entyvio package insert, 2022). As some UC patients may receive non-biologic medications during the course of their disease, a sensitivity analysis incorporating a non-biologic comparator cohort will be used to evaluate the study outcomes among a cohort of UC pregnancies that are treated with only non-biologic medications (more details related to the interpretation of results for this cohort is described in Section 9.9).

8. Research Question and Objectives

The overall aim of this study is to evaluate the safety of mirikizumab in pregnant women and their infants. To achieve this aim, there are 3 objectives:

Objective 1: To monitor the use of mirikizumab during pregnancy by describing the demographic and clinical characteristics of women who are exposed to mirikizumab during pregnancy.

Objective 2: To describe the occurrence of adverse pregnancy and infant outcomes of interest among women with UC (and infants linked to these women) who are exposed during pregnancy to:

- mirikizumab
- aTNFs
- vedolizumab, or
- ustekinumab

The adverse pregnancy and infant outcomes of interest include:

- primary outcome: MCM and
- secondary outcomes: SA, SB, PTB, SGA.

Objective 3: To compare the relative risk (risk ratio) of the adverse pregnancy and infant outcomes of interest among pregnant women with UC (and infants linked to these women) who are exposed to mirikizumab during pregnancy, compared to the following comparator groups of pregnant women with UC (and infants linked to these women) who are exposed during pregnancy to: 1) aTNFs, 2) vedolizumab, or 3) ustekinumab.

This objective will only be analysed if sufficient sample sizes of mirikizumab and comparator group exposed pregnancies for the pregnancy outcomes (SA, SB, PTB), and a sufficient number of exposed pregnancies with linked infants for the infant outcomes (MCM, SGA) are attained.

9. Research Methods

9.1. Study Design

9.1.1. Study Design Overview

This is an observational secondary database cohort study leveraging US administrative insurance claims data. Based on the data, pregnant mothers can be linked to their offspring for a subset of the pregnancies. Pregnancy outcomes will be evaluated on all pregnancies meeting the patient selection criteria, and infant outcomes will be evaluated on the infants from a subset of pregnancies where there is mother-infant linkage available. Additional information regarding this data source can be found in Section 9.4.

Target trial emulation (TTE) has been proposed as a framework to prevent certain biases in observational analyses including immortal time bias that could result from a failure to align eligibility, treatment assignment, and start of follow-up while also identifying situations where adequate emulation may not be possible using the data at hand. In order to align these 3 parameters and limit the related potential immortal time bias, this study will use a TTE framework that has been adapted for examining pregnancy related exposure and outcomes in observational secondary database studies by Hernández-Díaz et al. (2023).

An overview of the steps involved in this approach include:

- outlining the required components of the hypothetical target trial, and
- describing the analogous real-world data to be used to emulate each of the components in the hypothetical target trial.

Table 9.1 was adapted from Hernández-Díaz et al. (2023) and represents the operational definitions for this study applying the methodology used in emulating a pregnancy exposure trial:

- "Target Trial" column representing the specifications for the study design elements if a hypothetical randomised trial were conducted, and
- "Emulation" column representing the study design elements that are to be implemented in this study protocol using real-world data to emulate the target trial for comparative analyses using the HealthVerity MOM data.

Table 9.1. Operational Definitions Used to Emulate the Target Trial in Observational Data

Protocol Component	Hypothetical Target Trial	Emulation in Observational Data

Eligibility criteria (inclusion/exclusion criteria)	• Enrolment period: (26 Oct 2023 – 31 Dec 2030)
	• Pregnancy: multiple trials depending on relevant gestational age for each outcome
	  ○ Early pregnancy or first trimester trial ≤13 weeks GA (MCM
	  ○ Mid pregnancy trial <20 weeks GA (SA)
	  ○ Anytime during pregnancy trial (SGA, SB)
	  ○ Anytime during pregnancy prior to 37 weeks (PTB)
	• Diagnosis of UC
	• Maternal age 10-60 years
	• Enrolment in the healthcare system of interest for at least 6 months
		• The same eligibility criteria are applied to the real-world data study cohorts, with the addition of the following criteria required to create a pregnancy episode using administrative claims data:
		  ○ Enrolment in the healthcare system of interest for at least 6 months prior to LMP through end of pregnancy.
		• The eligibility criteria are identified using standardised codes (e.g., ICD-10-CM diagnosis or procedure codes) and enrolment files containing demographic and insurance enrolment data.
		• The same eligibility criteria with separate analyses for each outcome based on predefined clinically relevant exposure periods

Treatment strategies (exposures of interest and study cohorts)	Include 4 study arms • Mirikizumab (treatment arm) • Anti-tumour necrosis factor (comparator arm) • Vedolizumab (comparator arm) • Ustekinumab (comparator arm)	• Similar mirikizumab and comparator exposure cohorts are created based on pharmacy dispensings (NDC codes) and service or procedure codes (injection or infusion) (HCPCS codes) • Exposure assessment time periods are evaluated based on clinically relevant time periods (e.g., exposures for SA must occur prior to the outcome and SA must occur <20 weeks' gestational age). See Table 9.5 for all operational definitions of the study time periods.
Treatment assignment (based on clinically relevant definitions and assessment periods)	• Pregnancies are randomly assigned to one of the treatment cohorts.	• No randomisation • Baseline covariates balanced using PS methods
Outcomes (based on clinically relevant definitions and assessment periods)	Outcomes are measured based on clinically relevant outcome assessment periods: • MCM (measured during the 365 days after birth) • SGA (measured during the 30 days after birth) • SA (must occur <20 weeks' gestation) • Preterm delivery (must occur <37 weeks' gestation) • Stillbirth (must occur ≥20 weeks' gestation)	• The same outcomes are measured within clinically relevant time periods (e.g., exposures for SA must occur prior to the outcome and SA must occur <20 weeks' gestational age). See Table 9.5 in the protocol for all operational definitions of the study time periods. • Diagnoses are identified using algorithms based on combinations of standardised codes (e.g., ICD-10-CM diagnosis or relevant procedure codes) in the database

Follow-up	• Starts at treatment assignment • Ends at the earliest event including occurrence of outcome of interest using clinically relevant time periods (e.g., follow-up would end for SA at 20 weeks' gestation, death (maternal death for pregnancy outcomes, infant death for infant outcomes) or loss to follow-up	• Starts at time of first qualifying treatment exposure • Ends at the clinically relevant time period (see Table 9.5 for operational definitions). Because pregnancy status is ascertained by the end-of-pregnancy outcome, forcing a "complete case" for all pregnancies qualifying for the study, partial/truncated follow-up time is not possible and therefore not used in analysis.
Causal contrasts	• ITT effect • PP effect	• Observational analogue of ITT* effect • Observational analogue of PP** effect
Statistical analysis	• ITT analysis: estimate outcome risks in each group and compare them through risk ratios with adjustment for loss to follow-up. • PP analysis: same as ITT analysis with censoring at non-adherence and further adjustment for predictors of adherence and the outcome.	• Observational analogue of ITT analyses, except for restriction to pregnancies where outcomes are ascertained, which forces a "complete case" for all pregnancies qualifying for the study. • Relative risks • Sensitivity analysis will follow an observational analogue of PP approach excluding patients who switch to other treatments or are exposed to teratogens after start of follow up.

Abbreviations: GA = gestational age; HCPCS = Healthcare Common Procedure Coding System; ICD-10-CM = International Classifications of Disease, Tenth Revision, Clinical Modification; ITT = intention-to-treat; LMP = last menstrual period; MCM = major congenital malformations; NDC = National Drug Codes; PP = per protocol; PS = propensity scores; PTB = preterm birth; SA = spontaneous abortion; SB = stillbirth; SGA = small for gestational age; UC = ulcerative colitis.

* ITT: in a target trial, the intention-to-treat requires that patients assigned to a treatment group are kept in that group during the analysis, regardless of deviations from treatment assignment following randomisation. Similarly in this observational analogue, patients who begin follow-up in a mirikizumab-exposed or comparator treatment-exposed cohort are kept in those respective cohorts during the analysis regardless of whether there is evidence of treatment switch or not.

**PP: in a target trial, the per-protocol approach requires that patients are censored in the case of deviations from treatment assignment following randomisation. In this observational analogue, patients who switch to other treatments after the start of follow-up will be excluded entirely from the analysis (i.e., analysis of partial/truncated follow-up time is not possible given that all pregnancy episodes must have one of the pregnancy outcomes of interest given the algorithm used to identify pregnancy).

There will be five study cohorts (see Section 9.2.1) in this study. The first study cohort will be pregnant women with evidence of exposure to mirikizumab, regardless of whether or not they have a diagnosis of UC in their claims history (Objective 1). Within this cohort, a nested cohort of women with a diagnosis of UC who are exposed to mirikizumab during pregnancy will be generated for descriptive (Objective 2) and comparative analysis (Objective 3) purposes. Three separate comparator cohorts will include women with UC exposed to the following medication groups during pregnancy:

1) aTNF
2) vedolizumab, or
3) ustekinumab

These cohorts are further described in Section 9.2.1 and in Table 9.2 and Table 9.4.

The mirikizumab-exposed cohorts will not be mutually exclusive, as the mirikizumab UC cohort is a subset of the mirikizumab cohort. The three comparator cohorts will be mutually exclusive based on UC medication exposure because the pregnancy is assigned to the cohort associated with the first qualifying exposure. A single patient may contribute more than one pregnancy episode to a given cohort, and the unit of analysis will be each pregnancy episode. Objective 3 will be analysed if there is sufficient sample size of mirikizumab and comparator group exposed pregnancies for pregnancy outcomes, and sufficient number of women with linked infants for infant outcomes.

Pregnancy episodes will be created using a validated algorithm by Moll et al. (2021), which identifies the first day of the LMP (or date of LMP) and the date of the end of pregnancy (further described in Section 9.1.2). The date of LMP will be estimated to determine the pregnancy start date. In order for a pregnancy to be eligible for analysis in the database, 180 days of continuous enrolment prior to the start of the pregnancy episode through the end of the pregnancy episode (pregnancy episode details can be found in Section 9.1.2) will be required. Pregnancy episodes that start prior to the pregnancy identification period will not be included. Due to the length of the study period, it is possible that some women may have multiple pregnancy episodes across the years. The analysis will be conducted on a pregnancy episode level, not a patient level.

Exposure to mirikizumab and comparator group medications will be assessed based on prescription fills and/or medical claims for drug administration during the relevant time window for each pregnancy outcome of interest. Maternal use of the medication within 5 half-lives of the respective medication prior to the LMP will be used to determine exposure that may carry over into the pregnancy. Medication-specific half-life information can be found in Annex 1. Details related to exposure identification are described in Section 9.3.1. The relevant exposure window for mirikizumab and the comparator medication will be assessed for each respective outcome. For further information on exposure classification, see Section 9.3.1.

Pregnancy outcomes will be defined based on the presence of inpatient and/or outpatient diagnoses or procedure claims codes, and clinically relevant time windows will be used to define each outcome (see Table 9.5 in Section 9.2.2). The primary outcome of interest is MCM, where exposure in the first trimester is the most aetiologically relevant exposure window. Secondary outcomes include SA, SB, PTB, and SGA infants. See Section 9.3.2 for more detail on outcomes.

9.1.2. Identification of Pregnancies

9.1.2.1. Overview of Pregnancy Algorithm

The unit of analysis for this study will be the pregnancy episode. As such, one patient may be assessed multiple times for multiple pregnancy episodes. Pregnancy episodes will be identified on the basis of a validated multi-step algorithm that uses ICD-10-CM, ICD-10-PCS, CPT/HCPCS codes, and DRG code on the claims records (BEST 2020; Moll et al. 2021). The approach selected for this study to identify pregnancy episodes is a validated algorithm using ICD-10-CM/PCS codes and was developed in collaboration with the FDA (BEST 2020). This algorithm is now considered a “gold standard” for identifying pregnancy episodes using administrative claims data, because the algorithm to identify the start and end of the pregnancy along with the pregnancy-related outcomes has been validated using current diagnosis and procedure coding systems (ICD-10-CM). In addition, it provides an accurate estimate of

gestational age at the time of various events occurring during the pregnancy episode using LMP to calculate the gestational age. These attributes represent improvements over existing algorithms used to identify pregnancy milestones (Hornbrook et al. 2007; Cooper et al. 2008; Eworuke et al. 2012; Li et al. 2013; Matcho et al. 2018; He et al. 2020; Thurin et al. 2022). The algorithm was developed in US commercial claims data, using pregnancies between August 2016 and October 2018 and includes the pregnancy outcomes included in this study (SB, SA, PTB). The algorithm was validated against physician adjudication of electronic medical records, with the positive predictive agreement being 100% for SA and 70.8% for SB (BEST 2020). When stratifying by type of live birth, the positive predictive agreement was higher for full term deliveries (97.8%) than for preterm deliveries (62.4%). The estimated LMP date is also determined via the algorithm to be able to assign a pregnancy start date) and estimate gestational age at time of various events along the pregnancy timeline (BEST 2020). Ultimately, the algorithm produces a window of time from the start of the pregnancy, estimated by LMP, until the pregnancy end date. Code lists for the algorithm are included in Appendices A and K and details related to implementing the algorithm will be described in detail in the SAP.

Because of the hierarchy implemented in the algorithm, a patient can only be classified as having one pregnancy outcome and cannot qualify for more than one outcome for each pregnancy. Preterm and full-term births will be distinguished by gestational age; for pregnancies ending <37 weeks' gestational age the infant will be classified as preterm and full-term if gestational age is ≥37 weeks when the pregnancy ends. SB and SA will also be distinguished by gestational age; SB must occur at ≥20 weeks of gestation and SA must occur before 20 weeks of gestation.

9.1.2.2. Pregnancy Episode and Study Design Elements

The study by Moll et al. (2021) captures an entire pregnancy episode with various outcomes using claims data. The duration of the pregnancy episode will be dependent upon and constructed by each individual's available claims data as described in Section 9.1.2.3. Each qualifying pregnancy episode that meets all inclusion and exclusion criteria as described in Section 9.2.1 will be assessed for potential medication exposure occurring prior to pregnancy outcome. A patient may have multiple qualifying pregnancy episodes included in this study, because the unit of measurement for this study are the pregnancy episodes, not the patient.

Each pregnancy episode will be characterised into time periods of interest, including LMP, trimesters (as defined by estimated gestational age), and end of the pregnancy episode which will be used to anchor assessment windows throughout this study.

All pregnancy episodes eligible for this study will have a mutually exclusive pregnancy outcome at the end of their individual pregnancy episode which applies relevant gestational age restrictions and logic checks (see Section 9.1.2.3). Three of the five *study* outcomes are also pregnancy outcomes: SA, PTB, and SB. By default, these outcomes will be used to define the end of a pregnancy episode. The reasonableness of the estimated pregnancy episode start date and gestational age at the time of the outcome will be evaluated in order to ensure a sufficient amount of time has elapsed between pregnancy episodes. For instance, after identifying the first record indicating a live birth for a patient, the timing of the second live birth record will be assessed with respect to the first live birth to determine if a second pregnancy resulting in a live birth was biologically plausible within the time window. A brief description of the process is described below and additional details related to the algorithm to create pregnancy episodes and

identification of events (e.g., exposure to medications) will be explained in greater detail in the SAP.

9.1.2.3. Steps to Generate Pregnancy Episode

Step 1: Identification of any pregnancy outcome

Events indicating the occurrence of a pregnancy outcome as defined by Moll et al. (2021) (i.e., end of a pregnancy episode) will be identified across all healthcare settings (e.g.,` live births, stillbirths, etc.). It should be noted that the pregnancy outcomes of interest for this study are a subset of the outcomes used by Moll et al. (2021) to define the end of a pregnancy episode. Codes for identifying each outcome are provided in Appendix A. A hierarchical approach will be used starting with pregnancy outcomes considered the most reliably coded in claims data and is further described in the steps below.

Steps 2 and 3: Construction of pregnancy episodes from service records with pregnancy-related outcome codes

Because it is unknown if pregnancy outcomes identified for each patient in Step 1 are part of the same pregnancy or from a different pregnancy episode, it is necessary to identify distinct pregnancy episodes (e.g., the start and end of a pregnancy). In order to identify a pregnancy episode, the estimated LMP date and a pregnancy outcome date must be defined.

The end result is the identification of one or more pregnancy episodes for a patient. Next, a prenatal timeline will be constructed for each pregnancy episode, which includes all records between the date of the pregnancy outcome and the estimated earliest possible LMP.

Step 4: Assignment of gestational age and confirm final outcomes

A hierarchical algorithm will be used to estimate and assign the LMP dates, calculate gestational age at the time of the outcome, confirm the outcomes placed on the timeline in Step 2, and differentiate preterm births from full-term births (<37 vs. ≥37 weeks). The hierarchical algorithm includes utilising dates and gestational age indicated on claims for prenatal services including intrauterine insemination or embryo transfer, ultrasounds, nuchal translucency scans, anatomic ultrasounds, chorionic villus sampling and prenatal cell-free DNA screening, claims with codes indicating status of the pregnancy (claims documenting that the pregnancy had reached a certain trimester, was full-term or preterm status), glucose screening tests and other prenatal services.

At each level of the hierarchy, the reasonableness of the estimated pregnancy start date and gestational age at the time of the outcome will be evaluated. Gestational age in days at the time of the outcome will be calculated.

The SAP will contain detailed description of the pregnancy episode algorithm including code lists.

9.2. Setting

9.2.1. Study Population

Inclusion and exclusion criteria are outlined for all study cohorts in Table 9.2. Exposure assessment windows with respect to pregnancy episodes are described for all medications in Sections 9.2.2 and 9.3.1. Exposure to mirikizumab or comparator medications is defined in Section 9.3.1. Additional outcome-specific inclusion/exclusion criteria for study cohorts are described in Section 9.2.1.2. The start of pregnancy will be defined as the estimated date of LMP. Because insurance claims data do not contain LMP dates, a validated algorithm defined by Moll et al. (2021) (see Section 9.1.2) will be used to estimate LMP.

Table 9.2. Cohort Overview

Objective	Cohort	Start of Pregnancy	Exposure of Interest*	Rationale for Cohort
1 (descriptive)	Mirikizumab cohort (all mirikizumab-exposed)	LMP	Mirikizumab (irrespective of UC diagnosis or infant linkage)	Mirikizumab (IL-23 inhibitor) is the primary exposure of interest in this protocol. This cohort will be used for Objective 1, the monitoring of mirikizumab use during pregnancy.
2 and 3 (descriptive and comparative**)	Mirikizumab UC cohort (exposed)	LMP	Mirikizumab	Mirikizumab (IL-23 inhibitor) is the primary exposure of interest in this protocol. This cohort will be used for Objectives 2 (descriptive) and 3 (comparative)
	aTNF UC cohort (comparator)	LMP	Infliximab Adalimumab Golimumab	These biologics are indicated for the treatment of moderately-to-severely active UC and, as such, are relevant comparator cohorts.
	Vedolizumab UC cohort (comparator)	LMP	Vedolizumab	
	Ustekinumab UC cohort (comparator)	LMP	Ustekinumab	

Abbreviations: aTNF = anti-tumour necrosis factor; IL-23 = interleukin-23; LMP = last menstrual period; UC = ulcerative colitis.

* For Objectives 2 and 3, only the first qualifying medication exposure in the exposure assessment window is considered to qualify a pregnancy for each respective cohort.

** Objective 3 (comparative) will be analysed if there is sufficient sample size of mirikizumab and comparator group exposed pregnancies for pregnancy outcomes, and sufficient number of women with linked infants for infant outcomes.

9.2.1.1. Cohort for Objective 1: Mirikizumab Cohort

The mirikizumab cohort will include pregnancy episodes among women who are exposed to mirikizumab, irrespective of infant linkage or UC diagnosis. This cohort will be used for the assessment of Objective 1 (descriptive).

Inclusion criteria:

- Date of LMP occurring during the pregnancy identification period (see Section 9.2.2 for definition of the pregnancy identification period), identified following the algorithm described in Moll et al. (2021)
- Maternal age 10 to 60 years at pregnancy episode LMP
- Continuous enrolment (allowing ≤30 day-long gaps in enrolment) in the database from 180 days before LMP through the end of pregnancy
- Mirikizumab use (≥1 prescription or medical claim) during the pregnancy episode or within 5 half-lives prior to the LMP date

9.2.1.2. Cohorts for Objectives 2 and 3: Mirikizumab or Comparator Treatments Among Women Diagnosed with Ulcerative Colitis

For Objectives 2 and 3, mirikizumab or comparator exposure cohort assignment will be based on the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome-specific exposure assessment window (defined under Study Period below in the abstract and in Section 9.2.2). When the first qualifying exposure occurs during the 5 half-lives before LMP or on the LMP date, the start of follow-up begins at LMP. When the first qualifying exposure occurs after the LMP date the start of follow-up begins on the date of the first qualifying exposure. Women who are exposed to multiple UC biologic medications on the start of follow-up date will be excluded. Therefore, a pregnancy episode cannot qualify for more than one cohort. However, during the qualifying pregnancy episode, women who switch medication or are exposed to JAKi after the start of follow up, will be retained in the original cohort (i.e., observational analogue of an ITT approach).

For example, if the first cohort-defining medication exposure was for mirikizumab at 10 weeks' gestation and there was a switch to aTNF at 13 weeks' gestation, this pregnancy would be classified in the mirikizumab cohort. Pregnancy episodes can have concomitant non-biologic use at any time prior to or during the pregnancy episode.

Mirikizumab UC Cohort

The mirikizumab UC cohort will be a subset of the mirikizumab cohort restricting to pregnancy episodes among women with evidence of UC diagnosis and will be considered in the analysis of the Objectives 2 and 3. Pregnancy episodes in the mirikizumab UC cohort will be only those occurring among women with mirikizumab exposures as the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome-specific exposure assessment window.

Inclusion criteria:

- Date of LMP occurring during the pregnancy identification period (see Section 9.2.2)
- Maternal age 10 to 60 years at LMP
    - Note: patients must be age ≥14 years to be able to be linked with an infant in HealthVerity MOM database
- Continuous enrolment (allowing ≤30 day-long gaps in enrolment) in the database from 180 days before LMP through the end of pregnancy
- Mirikizumab exposure (≥1 prescription or medical claim) as the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome-specific exposure assessment window.
    - Note: Exposure assessment windows are defined in Section 9.2.2 and details regarding the use of information available on prescription and medical claims for determining whether or not the pregnancy is exposed is provided in Section 9.3.1. Exposure to mirikizumab occurring after the end of pregnancy (defined by pregnancy outcomes), will not be considered to be within the exposure assessment window.
- At least one diagnosis code for UC (ICD-10-CM K51*) (Ogino et al. 2022) in any position of the claims record from any time prior to LMP until the start of the first prescription or medical claim for mirikizumab but before the end of the pregnancy episode
    - Note: Pregnancy episodes with a concurrent diagnosis for CD are still eligible for inclusion. A sensitivity analysis will be conducted excluding pregnancy episodes with diagnosis codes for both UC and CD (see Section 9.7.3.3).

Exclusion criteria

- Evidence of teratogen exposure as identified in claims data (see Appendix D for a list of examples of potential teratogens and corresponding half-lives). Identification of exposure to teratogens will be based upon prescription fills and medical encounter claims and will be considered exposed if used within 5 half-lives of the respective teratogen prior to LMP until the first qualifying mirikizumab exposure
- Exposure to JAKi (>1 prescription or medical claim) in the 5 half-lives prior to LMP until the first qualifying mirikizumab exposure.
- Pregnancy episodes qualifying for more than one cohort (mirikizumab or comparator cohorts) (See Section 9.3.1).

Comparator cohorts

Three separate comparator cohorts of interest will be created for Objectives 2 and 3: the aTNF UC cohort, the vedolizumab UC cohort, and the ustekinumab UC cohort. Pregnancy episodes in the comparator UC cohort will be those occurring among women with the comparator medication exposure as the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome-specific exposure assessment window.

The aTNF UC cohort

Inclusion criteria:

- Date of LMP occurring during the pregnancy identification period (see Section 9.2.2)

- Maternal age 10 to 60 years at LMP
    - Note: patients must be age ≥14 years to be able to be linked with an infant in HealthVerity MOM database
- Continuous enrolment (allowing ≤30 day-long gaps in enrolment) in the database from 180 days before LMP through the end of pregnancy
- Exposure to one of the aTNF medications of interest (≥1 prescription or medical claim, see Table 9.2 for list of medications of interest) as the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome-specific exposure assessment window.
    - Note: Exposure assessment windows are defined in Section 9.2.2 and details regarding the use of information available on prescription and medical claims for determining whether or not the pregnancy is exposed is provided in Section 9.3.1. Exposure to aTNF occurring after the end of pregnancy (defined by pregnancy outcomes), will not be considered to be within the exposure assessment window.
- At least one diagnosis code for UC (ICD-10-CM K51*) (Ogino et al. 2022) in any position of the claims record from any time prior to LMP until the start of the first prescription or medical claim for a qualifying aTNF medication but before the end of the pregnancy episode
    - Note: Pregnancy episodes with a concurrent diagnosis for CD are still eligible for inclusion. A sensitivity analysis will be conducted excluding pregnancy episodes with diagnosis codes for both UC and CD (see Section 9.7.3.2).

Exclusion criteria:

- Evidence of teratogen exposure as identified in claims data (see Appendix D for a list of examples of potential teratogens and corresponding half-lives). Identification of exposure to teratogens will be based upon prescription fills and medical encounter claims and will be considered exposed if used within 5 half-lives of the respective teratogen prior to LMP until the first qualifying aTNF exposure.
- Diagnosis (≥1 medical claim) of any of the other indications for aTNF medications of interest (see Table 9.3) any time prior to LMP until the first qualifying aTNF exposure (see Table 9.4).
- Exposure to JAKi (>1 prescription or medical claim) in the 5 half-lives prior to LMP until the first qualifying TNF exposure
- Pregnancy episodes qualifying for more than one cohort (See Section 9.3.1)

The vedolizumab UC cohort

Inclusion criteria:

- Date of LMP occurring during the pregnancy identification period (see Section 9.2.2)
- Maternal age 10 to 60 years years at LMP
    - Note: patients must be age ≥14 years to be able to be linked with an infant in HealthVerity MOM database
- Continuous enrolment (allowing ≤30 day-long gaps in enrolment) in the database from 180 days before LMP through the end of pregnancy

- Vedolizumab exposure (≥1 prescription or medical claim) as the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome-specific exposure assessment window.
    - Note: Exposure assessment windows are defined in Section 9.2.2 and details regarding the use of information available on prescription and medical claims for determining whether or not the pregnancy is exposed is provided in Section 9.3.1. Exposure to vedolizumab occurring after the end of pregnancy (defined by pregnancy outcomes), will not be considered to be within the exposure assessment window.
- At least one diagnosis code for UC (ICD-10-CM K51*) (Ogino et al. 2022) in any position of the claims record from any time prior to LMP until the start of the first prescription or medical claim for vedolizumab but before the end of the pregnancy episode
    - Note: Pregnancy episodes with a concurrent diagnosis for CD are still eligible for inclusion. A sensitivity analysis will be conducted excluding pregnancy episodes with diagnosis codes for both UC and CD (see Section 9.7.3.2)

Exclusion criteria

- Evidence of teratogen exposure as identified in claims data (see Appendix D for a list of examples of potential teratogens and corresponding half-lives). Identification of exposure to teratogens will be based upon prescription fills and medical encounter claims and will be considered exposed if use is possible within 5 half-lives of the respective teratogen prior to LMP until the first qualifying vedolizumab exposure
- Diagnosis (≥1 medical claim) of any of the other indications for vedolizumab (see Table 9.3) any time prior to LMP until the first qualifying vedolizumab exposure (see Table 9.4)
- Exposure to JAKi (>1 prescription or medical claim) in the 5 half-lives prior to LMP until the first qualifying vedolizumab exposure
- Pregnancy episodes qualifying for more than one cohort (See Section 9.3.1)

The ustekinumab UC cohort

Inclusion criteria:

- Date of LMP occurring during the pregnancy identification period (see Section 9.2.2)
- Maternal age 10 to 60 years at LMP
    - Note: patients must be age ≥14 years to be able to be linked with an infant in HealthVerity MOM database
- Continuous enrolment (allowing ≤30 day-long gaps in enrolment) in the database from 180 days before LMP through the end of pregnancy
- Ustekinumab exposure (≥1 prescription or medical claim) as the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome-specific exposure assessment window

  - Note: Exposure assessment windows are defined in Section 9.2.2 and details regarding the use of information available on prescription and medical claims for determining whether or not the pregnancy is exposed is provided in Section 9.3.1. Exposure to ustekinumab occurring after the end of pregnancy (defined by pregnancy outcomes), will not be considered to be within the exposure assessment window.
- At least one diagnosis code for UC (ICD-10-CM K51*) (Ogino et al. 2022) in any position of the claims record from any time prior to LMP until the start of the first prescription or medical claim for ustekinumab but before the end of the pregnancy episode
  - Note: Pregnancy episodes with a concurrent diagnosis for CD are still eligible for inclusion. A sensitivity analysis will be conducted excluding pregnancy episodes with diagnosis codes for both UC and Crohn's disease (CD) (see Section 9.7.3.2)

Exclusion criteria

- Evidence of teratogen exposure as identified in claims data (see Appendix D for a list of examples of potential teratogens and corresponding half-lives). Identification of exposure to teratogens will be based upon prescription fills and medical encounter claims and will be considered exposed if use is possible within 5 half-lives of the respective teratogen prior to LMP until the first qualifying ustekinumab exposure
- Diagnosis (≥1 medical claim) of any of the other indications for ustekinumab (see Table 9.3) any time prior to LMP until the first qualifying ustekinumab exposure (see Table 9.4)
- Exposure to JAKi (>1 prescription or medical claim) in the 5 half-lives prior to LMP until the first qualifying ustekinumab exposure
- Pregnancy episodes qualifying for more than one cohort (See Section 9.3.1)

Table 9.3. Other Indications to Exclude by Comparator Group

Comparator Group	Other indications
aTNF	Plaque psoriasis Rheumatoid arthritis (RA) Ankylosing spondylitis Psoriatic arthritis (PsA) Juvenile idiopathic arthritis (JIA) Hidradenitis suppurativa (HS) Uveitis (UV)
Ustekinumab	Plaque psoriasis PsA CD

Abbreviations: aTNF = anti-tumour necrosis factor; CD = Crohn's disease.

Inclusion criteria applied by outcome:

For Objectives 2 and 3 only, additional specific inclusion criteria will be applied by outcome (see Table 9.4). Outcome-specific assessment windows for exposures are defined separately for mirikizumab and for each comparator group to account for drug-specific half-lives and outcome-specific aetiology. Pregnancy episodes selected for inclusion in outcome-specific analytic cohorts must satisfy the criteria below. For all pregnancy episodes, the LMP date must occur at least 37 weeks (i.e., the duration of a full-term pregnancy) prior to the end of the study period to avoid potential biases related to overrepresentation of shorter pregnancies and their respective pregnancy outcomes, such as SA and PTB, towards the end of the study period. For MCM and

SGA outcomes, additional specific LMP date requirements are outlined in Table 9.4. Maternal medical and pharmacy claims will be used to assess exposures for each outcome.

Note: While mother-infant linkage is required for inclusion in the infant outcome cohorts (MCM and SGA), it is *not* required for the pregnancy outcome cohorts (SB, PTB, and SA).

Table 9.4. Outcome-Specific Exposure Assessment Windows and Inclusion Criteria for Objectives 2 and 3

Outcome	Additional Inclusion Criteria and Exposure Assessment Window
Major congenital malformations (MCM)	• Pregnancy outcome is a live birth delivery • Infant claims data available through mother-infant linkage to the pregnancy • To allow for the opportunity for 1 year of infant follow-up, the LMP date must occur at least 365 days plus the duration of a full-term pregnancy (defined as ≥37 weeks of gestation) prior to the end of study period, (see Section 9.2.2 for additional detail) and the infant must have medical claims enrolment on at least the date of birth and the subsequent day • Exposure to mirikizumab or comparator medications will be assessed in the period starting 5 half-lives (specified in Annex 1) prior to LMP until the end of the first trimester. See Section 9.3.1 for further detail.
Small for gestational age (SGA)	• Pregnancy outcome is a live birth delivery • Infant claims data available through mother-infant linkage to the pregnancy • To allow for the opportunity for 30 days infant follow-up, the LMP date must occur at least 30 days plus the duration of a full-term pregnancy (defined as ≥37 weeks of gestation) prior to the end of study period, (see Section 9.2.2 for additional detail) and the infant must have medical claims enrolment on at least the date of birth and the subsequent day • Exposure to mirikizumab or comparator medications will be assessed in the period starting 5 half-lives (specified in Annex 1) prior to LMP until the end of the pregnancy episode. See Section 9.3.1 for further detail.
Stillbirth (SB)	• Pregnancy is ≥20 weeks' gestation • LMP date must occur at least 37 weeks (duration of a full-term pregnancy) prior to the end of study period (see Section 9.2.2 for additional detail). • Exposure to mirikizumab or comparator medications will be assessed in the period starting 5 half-lives (specified in Annex 1) prior to LMP until the end of the pregnancy. See Section 9.3.1 for further detail. • Exposure must occur prior to the outcome
Preterm birth (PTB)	• Pregnancy is ≥22 weeks' gestation and ends in live birth delivery • LMP date must occur at least 37 weeks (duration of a full-term pregnancy) prior to the end of study period (see Section 9.2.2 for additional detail). • Exposure to mirikizumab or comparator medications will be assessed in the period starting 5 half-lives (specified in Annex 1) prior to LMP until <37 weeks' gestation. See Section 9.3.1 for further detail. • Exposure must occur prior to the outcome
Spontaneous abortion (SA)	• Exposure occurs <20 weeks' gestation • LMP date must occur at least 37 weeks (duration of a full-term pregnancy) prior to the end of study period (see Section 9.2.2 for additional detail). • Exposure to mirikizumab or comparator medications will be assessed in the period starting 5 half-lives (specified in Annex 1) prior to LMP until <20 weeks' gestation. See Section 9.3.1 for further detail. • Exposure must occur prior to the outcome

Abbreviations: LMP = last menstrual period.

9.2.1.3. Subgroups and Stratifications

Stratified analyses will be conducted for Objectives 2 and 3. Comparative analyses of Objective 3 will be performed for the strata listed below if there is a minimum of 307 pregnancies in each of the mirikizumab-exposed and comparator medication-exposed cohorts. This sample size threshold is based on the minimum number of observations needed to achieve a confidence interval width of 4 for a minimum detectable RR of at least 2.5 (1.21, 5.21) between mirikizumab-exposed and comparator groups for the primary outcome of MCM. The following stratifications will be evaluated separately and for all outcomes.

Exposure stratification:
Analyses will be stratified by trimester of first exposure by first, second and third trimesters. The first qualifying exposure for each pregnancy will be classified as follows:

- first trimester is exposure between LMP through 13 weeks' and 6 days' gestation
- second trimester exposure is considered to begin at 14 weeks 0 days after LMP and continues through 27 weeks and 6 days after LMP, and
- third trimester exposure is considered to begin at 28 weeks 0 days after LMP through 40 weeks and 6 days after LMP.

9.2.2. Study Period

The source population for this study consists of the study population within the HealthVerity MOM database with pharmacy and medical benefits. The relevant periods within the study are outlined in Figure 9.1, Figure 9.2, and Figure 9.3, Figure ANN.4.1, Figure ANN.4.2, and Figure ANN.4.3, and are further described below.

- **Study period:** The entire study period includes data from the start of available data, 01 January 2008 through the end of data on 31 December 2030. The HealthVerity MOM database contains information on pregnancies starting from 01 January 2018 and historical medical and pharmacy claims information on these pregnant women starting 01 January 2008 (start of available data in the study database).
- **Pregnancy identification period**: Starts on 26 October 2023 (the date of mirikizumab approval in the US) through the end of data collection on 31 December 2030. Pregnancy episodes that start before the pregnancy identification period will not be eligible for inclusion in the study.
- **Exposure assessment window:** The time window in which the exposure is assessed varies by outcome as follows. Additional details regarding exposure assessment windows are described in Table 9.6 and Annex 1:
    - For MCM outcomes, the exposure assessment period is from 5 half-lives prior to LMP until the end of the first trimester. Exposure in the first trimester of pregnancy is the relevant exposure window for analysis of MCM, as this is the time when major body organs and systems are developing.
    - For SA outcomes, the exposure assessment period is from 5 half-lives prior to LMP until <20 weeks (i.e., 19 weeks and 6 days) of gestation

  - For PTB, the exposure assessment period is from 5 half-lives prior to LMP until <37 weeks (i.e., 36 weeks and 6 days) of gestation
  - For SGA and SB, the exposure assessment period is from 5 half-lives prior to LMP until the end of the pregnancy.

- **Teratogen assessment window:** Exposure to teratogens will be assessed based on pharmacy and/or medical claims for the respective medication for both the mirikizumab UC cohort as well as all comparator cohorts for all study outcomes. This will consider possible use of medication within 5 half-lives of the respective medication prior to the LMP until the first qualifying exposure to mirikizumab or comparator medication.
- **Continuous enrolment period:** Continuous enrolment with 30-day allowable gaps is required starting 180 days prior to LMP to the end of the pregnancy episode. For the analysis of MCM and SGA outcomes, linked infants will be required to have medical claims enrolment on at least the date of birth and the subsequent day.
- **Ulcerative colitis diagnosis period:** All time prior to LMP up until the first qualifying medication exposure but before the end of the pregnancy episode, during which mothers are required to have a diagnosis of UC qualifying the pregnancy to be included in the analysis of Objectives 2 and 3.
- **Other indications exclusions period:** All time prior to LMP up until the first qualifying medication exposure, during which mothers will be assessed for medication group-specific diagnoses related to other indications for the medications in the study (see Table 9.3). Any pregnant women with other indications in this time period will be excluded (i.e., only pregnancy episodes during which evidence of another indication of interest is present will be excluded).
- **Covariate assessment window:** The covariate assessment window varies by covariate and is further described in Table 9.8 in Section 9.3.3.
- **Pregnancy outcome follow-up periods:** For all pregnancy outcomes, the outcome must occur after the first qualifying exposure.
  - Start of Follow-Up:
    - For the analysis of all study outcomes, if the first qualifying medication exposure occurs on the LMP date or during the 5 half-lives before LMP date, the start of follow-up will begin on the LMP date. If the first qualifying medication exposure occurs after LMP date, the start of follow-up will begin on the date of the first qualifying medication exposure.
  - Outcome Assessment Windows:
    - For the analysis of SB, if the first qualifying exposure occurs on the LMP date, during the 5 half-lives prior to LMP, or after LMP but before 20 weeks' gestation, then the outcome assessment window will begin at 20 weeks' gestation and end at the earliest occurrence of a SB or end of the pregnancy episode. If the first qualifying exposure occurs on or after 20 weeks' gestation, then the outcome assessment window will begin on the

date of first qualifying exposure and end at the earliest occurrence of a SB or end of the pregnancy episode.

- For the analysis of the SA, if the first qualifying exposure occurs on LMP date or during the 5 half-lives before LMP date, the outcome assessment window will begin at the LMP date and end at the occurrence of a SA, 20 weeks' gestation or end of the pregnancy episode, whichever occurs first. If the first qualifying exposure occurs after the LMP date and before 20 weeks' gestation, the outcome assessment window will begin on the date of first qualifying exposure and end at the occurrence a SA, of 20 weeks' gestation or end of the pregnancy episode, whichever occurs first.
- For the analysis of PTB, if the first qualifying exposure occurs on the LMP date, during the 5 half-lives before the LMP date, or after the LMP date but before 22 weeks' gestation, the outcome assessment window will begin at 22 weeks' gestation and end at the occurrence of PTB, 37 weeks' gestation, or the end of the pregnancy episode, whichever occurs first. If the first qualifying exposure occurs after the LMP date and on or after 22 weeks' gestation, but before 37 weeks' gestation, the outcome assessment window will begin on the date of first qualifying exposure and end at the occurrence of PTB, 37 weeks' gestation, or the end of the pregnancy episode, whichever occurs first.

- **Infant outcome follow-up periods:** For all infant outcomes, the outcome must occur after the first qualifying exposure.
  - *Follow-up for the assessment of MCM*: MCMs will be evaluated two different ways: as a composite outcome (presence of at least one MCM) and by organ class (presence of at least one MCM within that specified organ class). The EUROCAT classification scheme will be used to define organ class (EC 2022). The details of the algorithms to define MCM (e.g., code lists and specific organ classes used by EUROCAT) will be detailed in the study SAP document. Each infant is eligible to experience more than one MCM outcome. In other words, if an infant has more than one MCM in different organ-level classes, it will count once in each organ-level category. However, infants with multiple MCMs will only contribute once to the composite outcome assessment. For the composite MCM outcome, infants will be followed from birth until the occurrence of either an MCM diagnosis, 365 days of follow-up, infant disenrollment (≤30-day gaps allowed, infant death, or end of the study period, whichever occurs first. For the organ-specific MCM outcomes, infants will be followed from birth until the occurrence of an MCM diagnosis, 365 days of follow-up, infant disenrollment (≤30-day gaps allowed), infant death, or the end of the study period, whichever comes first.

    While the occurrence of MCM is often diagnosed at birth, infants will be followed for up to 365 days to allow sufficient opportunity for these outcomes to be diagnosed and captured in the infant claims data. If the LMP date occurs less than 365 days + the duration of a full-term pregnancy, prior to the end of the study period, the infant will not be included in the analyses of the MCM outcomes. This exclusion criteria will be imposed to ensure that all infants have the *opportunity*

for a full-term pregnancy and 1 year of infant follow-up after birth. This addresses bias related to overrepresentation of shorter pregnancies towards the end of the study period and the potential bias that may result from the fact that infants born later in calendar time will systematically have less opportunity to have MCM detected in their claims. However, 365 days of continuous enrolment and follow-up will not be *required*.

- *Follow-up for the assessment of SGA*: SGA is assessed in the 30 days after birth until the occurrence of either an SGA outcome, 30 days of follow-up, infant disenrollment, infant death, or end of study period, whichever occurs first. SGA is typically diagnosed at or close to the time of birth, and thus following infants for up to 30 days allows sufficient opportunity for the outcome to be diagnosed and recorded on the infant claim. If the LMP date occurs less than 30 days + the duration of a full-term pregnancy prior to the end of the study period, the infant will not be included in the analyses of SGA outcomes. This exclusion criteria will be imposed to ensure that all infants have the *opportunity* for a full-term pregnancy and 30 days of infant follow-up after birth. This addresses bias related to overrepresentation of shorter pregnancies towards the end of the study period and the potential bias that may result from the fact that infants born later in calendar time will systematically have less opportunity to have SGA detected in their claims. However, 30 days of continuous enrolment and follow-up will not be *required*.

Table 9.5. Study Time Periods by Outcome

Outcome	Eligible Pregnancies	Exposure Assessment Windows	Baseline Period	Start of Follow-Up	Outcome Assessment Period
Pregnancy Outcomes					
Spontaneous Abortions	All pregnancies with first qualifying exposure occurring prior to 20 weeks' gestation and that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4	5 half-lives prior to the LMP date until <20 weeks' gestation	180 days prior to LMP up to date of first qualifying exposure	If the first qualifying exposure occurs on the LMP date or during the 5 half-lives before the LMP date, the start of follow-up begins on the LMP date. or If the first qualifying exposure occurs after the LMP date and before 20 weeks' gestation, the start of follow-up begins on the date of the first qualifying exposure.	For the analysis of the SA, if the first qualifying exposure occurs on LMP or during the 5 half-lives before LMP, the outcome assessment window will begin at LMP and end at the occurrence of a SA, 20 weeks' gestation or end of the pregnancy episode, whichever occurs first. If the first qualifying exposure occurs after LMP and before 20 weeks' gestation, the outcome assessment window will begin on the date of first qualifying exposure and end at the occurrence of a SA, 20 weeks' gestation or end of the pregnancy

Outcome	Eligible Pregnancies	Exposure Assessment Windows	Baseline Period	Start of Follow-Up	Outcome Assessment Period
					episode, whichever occurs first.
Stillbirths	Pregnancies with a gestational age of ≥20 weeks that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.	5 half-lives prior to the LMP date until the end of the pregnancy episode	180 days prior to LMP up to date of first qualifying exposure	If the first qualifying exposure occurs on the LMP date or during the 5 half-lives before LMP, the start of follow-up begins on the LMP date. or If the first qualifying exposure occurs after the LMP, the start of follow-up begins on the date of the first qualifying exposure.	For the analysis of SB, if the first qualifying exposure occurs on LMP, during the 5 half-lives prior to LMP, or after LMP but before 20 weeks' gestation, then the outcome assessment window will begin at 20 weeks' gestation and end at the occurrence of a SB or end of the pregnancy episode, whichever occurs first. If the first qualifying exposure occurs on or after 20 weeks' gestation, then the outcome assessment window will begin on the date of first qualifying exposure and end at the occurrence of a SB or end of the pregnancy

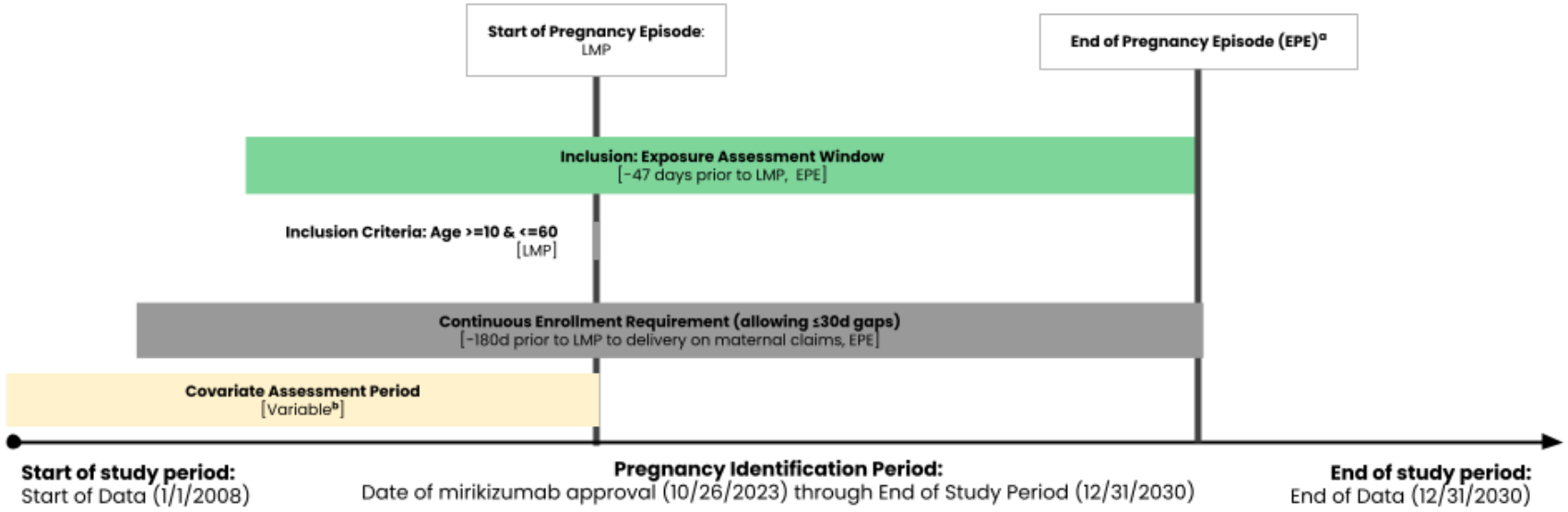
Outcome	Eligible Pregnancies	Exposure Assessment Windows	Baseline Period	Start of Follow-Up	Outcome Assessment Period
					episode, whichever occurs first.
Preterm Births	Pregnancies ending in a live birth with a gestational age ≥22 weeks with first qualifying exposure occurring on or prior to 37 weeks' gestation that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.	5 half-lives prior to the LMP date until <37 weeks' gestation	180 days prior to LMP up to date of first qualifying exposure	If the first qualifying exposure occurs on the LMP date or during the 5 half-lives before LMP, the start of follow-up begins on the LMP date. or If the first qualifying exposure occurs after the LMP and before 37 weeks' gestation, the start of follow- up begins on the date of the first qualifying exposure.	For the analysis of PTB, if the first qualifying exposure occurs on LMP, during the 5 half-lives before LMP, or after LMP but before 22 weeks' gestation, the outcome assessment window will begin at 22 weeks' gestation and end at the earliest of PTB, 37 weeks' gestation or the end of the pregnancy episode, whichever occurs first. If the first qualifying exposure occurs after LMP and on or after 22 weeks' gestation but before 37 weeks' gestation, the outcome assessment window begins on the date of first qualifying exposure and ends at

Outcome	Eligible Pregnancies	Exposure Assessment Windows	Baseline Period	Start of Follow-Up	Outcome Assessment Period
					the occurrence of PTB, 37 weeks' gestation or the end of the pregnancy episode, whichever occurs first.
Infant Outcomes					
Major Congenital Malformations	Pregnancies ending in live births with linked infant data that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.	5 half-lives prior to the LMP date until the end of first trimester*	180 days prior to LMP up to date of first qualifying exposure	If the first qualifying exposure occurs on the LMP date or during the 5 half-lives before LMP, the start of follow-up begins on the LMP date. or If the first qualifying exposure occurs after the LMP, the start of follow-up begins on the date of the first qualifying exposure.	For the composite MCM outcome, MCMs are assessed from birth until the occurrence of either an MCM diagnosis, 365 days, infant disenrollment, infant death, or end of the study period, whichever occurs first. For the organ-specific MCM outcomes, MCMs are assessed from birth until the occurrence of either an MCM diagnosis, 365 days, infant disenrollment, infant death, or end of the study period, whichever occurs first.

Outcome	Eligible Pregnancies	Exposure Assessment Windows	Baseline Period	Start of Follow-Up	Outcome Assessment Period
Small for Gestational Age	Pregnancies ending in live births with linked infant data that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.	5 half-lives prior to the LMP date until the end of pregnancy	180 days prior to LMP up to date of first qualifying exposure	LMP date: if the first qualifying exposure occurs on the LMP date or during the 5 half-lives before LMP or Date of the first qualifying exposure: if the first qualifying exposure occurs after the LMP	SGA is assessed in the 30 days after birth. Infants will be followed from birth until the occurrence of either an SGA outcome, 30 days, infant disenrollment, infant death, or the end of the study period, whichever comes first.

Abbreviation: LMP = last menstrual period; MCM = major congenital malformations; PTB = preterm birth; SA = spontaneous abortion; SB = stillbirth; SGA = small for gestational age.

* Exposure in the first trimester of pregnancy is the relevant exposure window for analysis of MCM, as this is the time when major body organs and systems are developing.

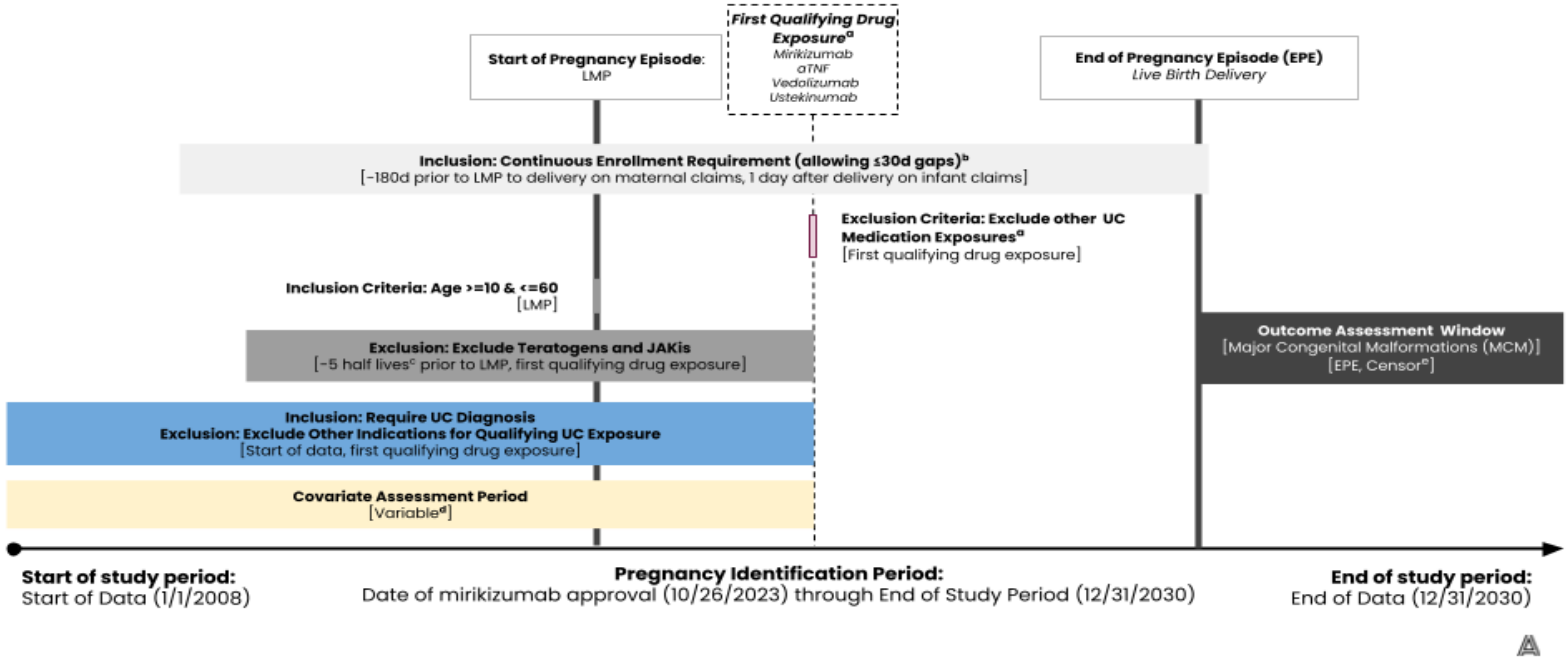


[a] The end of pregnancy episode is a pregnancy outcome defined by Moll et al (2021). Each pregnancy episode length may vary. For more information, see Section 9.1.2.

[b] Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table ANN.4.1.

Figure 9.1. Study design: Objective 1 (overall mirikizumab cohort).

Figure 9.2 and Figure 9.3 demonstrate two example pregnancy episodes with a mirikizumab or comparator UC medication exposure occurring in the exposure assessment window for the MCM outcome. Figure 9.2 demonstrates a pregnancy episode where the patient is exposed to the cohort defining-medication in the 5 half-lives prior to LMP. Figure 9.3 demonstrates a pregnancy episode where the patient is exposed to the cohort-defining medication after LMP, but prior to the end of the exposure assessment window for MCM. See Annex 4 for examples of non-MCM outcomes.



Abbreviations: aTNF = anti-tumour necrosis factor; JAKi = Janus kinase inhibitor; LMP = last day of menstrual period; UC = ulcerative colitis.

[a] The first qualifying drug exposure during the exposure assessment window is the exposure that determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with more than one UC exposure on the first qualifying exposure date will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF are started on the same day would not qualify and would therefore be excluded from this study.

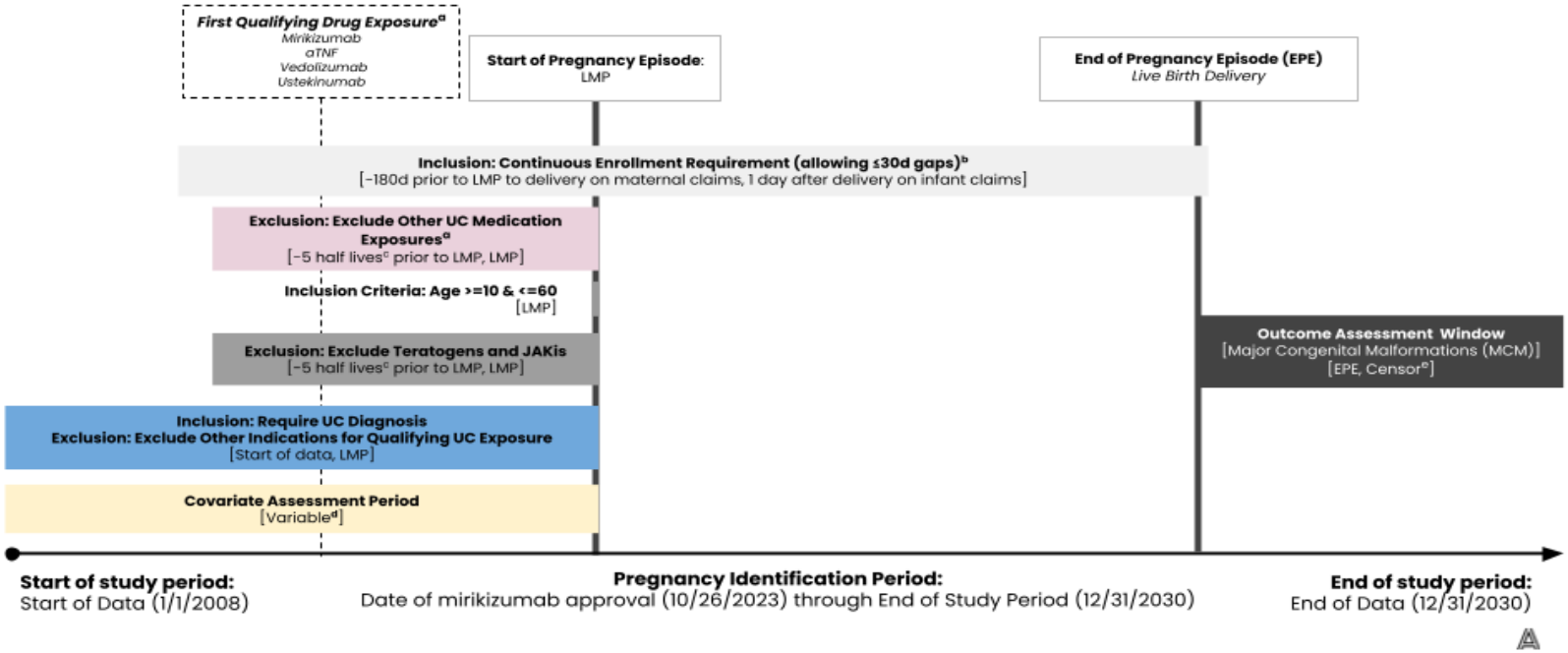
[b] The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

[c] The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

[d] Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

[e] All pregnancy episodes must end in a Live Birth to be assessed for this outcome. Mother-infant linkage is also required, and LMP must occur 365 days + duration of a full-term pregnancy prior to the end of data for this outcome. Major congenital malformation are assessed on infant claims from birth until the occurrence of either an MCM diagnosis, 365 days, infant disenrollment (≤30 day gaps allowed), infant death, or end of study period, whichever comes first.

Figure 9.2. Study design for assessment of the primary outcome of major congenital malformations (Objectives 2 and 3) where the first qualifying exposure is during pregnancy episode.



Abbreviations: aTNF = anti-tumour necrosis factor; JAKi = Janus kinase inhibitor; LMP = last day of menstrual period; UC = ulcerative colitis.

[a] The first qualifying drug exposure in the exposure assessment window determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with more than one UC medication exposure in the 5 half-lives prior to LMP will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF occur in the 5 half-lives prior to LMP cannot qualify for any cohort and would therefore be excluded from this study.

[b] The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

[c] The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

[d] Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

[e] All pregnancy episodes must end in a Live Birth to be assessed for this outcome. Mother-infant linkage is also required, and LMP date must occur at least 365 + the duration of a full-term pregnancy prior to the end of data for this outcome. Major congenital malformations are assessed on infant claims from birth until the occurrence of an MCM diagnosis, 365 days, infant disenrollment (≤30 day gaps allowed), infant death, or end of the study period, whichever occurs first.

Figure 9.3. Study design for assessment of the primary outcome of major congenital malformations (Objectives 2 and 3) where the first qualifying exposure occurs in 5 half-lives prior to LMP.

9.3. Variables

9.3.1. Exposure

Exposure Assessment:

A pregnancy episode will be considered exposed to mirikizumab or a comparator medication based on information recorded in the prescription and medical claims. In order for a pregnancy episode (defined as the first day of LMP up until end of pregnancy) to be classified as exposed to mirikizumab or a comparator medication, the first qualifying exposure to mirikizumab or a comparator drug must occur during one of the exposure assessment windows outlined under *Exposure Assessment Window* below.

Exposure for the mirikizumab-exposed cohorts (mirikizumab and mirikizumab UC) is defined as mirikizumab use and exposures for the comparator groups are defined as use of one of the following medications: aTNF, vedolizumab, or ustekinumab, For Objectives 2 and 3, mirikizumab or comparator exposure cohort assignment will be based on the first qualifying medication exposure that occurs during the 5 half-lives before the LMP date, on the LMP date, or during the pregnancy after LMP but within the relevant outcome specific exposure assessment window will determine the cohort assignment (e.g., mirikizumab or a comparator cohort). When the first qualifying exposure occurs during the 5 half-lives before LMP or on the LMP date, the start of follow-up begins at LMP. When the first qualifying exposure occurs after the LMP date the start of follow-up begins on the date of the first qualifying exposure. Women who are exposed to multiple UC medications on the start of follow-up date will be excluded.

Pharmacy claims will be used to identify prescription fills for medications dispensed through pharmacies and will include NDCs and/or generic drug names. Additional information recorded on the pharmacy claims (e.g., days supply) will be used to determine medication on hand. Intravenous administration or medical administrations of medications will be identified through medical claims using CPT/HCPCS codes or ICD procedure codes. In the case of mirikizumab, patients initiating mirikizumab may receive an induction dose IV from a healthcare provider, followed by SC maintenance doses dispensed through the pharmacy. In this case, the IV administrations would be billed through medical claims using HCPCS codes and the SC administrations would be billed through pharmacy claims using NDC codes. There can be a gap between when a new IV drug is approved and when it receives its specific HCPCS code. During this gap time, a non-specific HCPCs code is used for billing purposes. The unavailability of a mirikizumab-specific HCPCS code or ICD procedure code on medical claims may affect the ascertainment of exposure. Detailed information will be presented in the SAP to define how initiation of treatment will be defined if a non-specific HCPCs for an IV administration is used. Generally, for claims where a non-specific HCPCs code for IV administration of mirikizumab is used (i.e., for induction therapy), there will need to be an accompanying pharmacy claim for mirikizumab (i.e., for maintenance therapy) to be able to assign patients to a mirikizumab-exposed cohort.

Exposure Assessment Windows:

Exposures occurring on the LMP date, during the 5 half-lives (of each respective drug) prior to LMP or during the pregnancy episode after LMP may qualify a pregnancy episode for cohort inclusion. The half-life of each exposure medication will be considered in the construction of the

exposure assessment window (see Annex 1 for medication-specific half-lives). To determine potential foetal exposure to maternal medication use, maternal use of the medication within 5 half-lives of the respective medication prior to the LMP will be used to determine exposures that may carry over into the pregnancy.

The half-life of mirikizumab is 9.3 days; therefore, 5 half-lives to allow for elimination of exposure is approximately 47 days (Friedrich et al. 2023). This mirikizumab exposure window will be used whether mirikizumab is being used as induction or maintenance therapy. This conservatively considers exposure based on possible medication on hand (for example, uses the day's supply to estimate the number of days of possible exposure instead of using only the prescription fill date) and uses LMP to define the start of pregnancy episode. For the half-lives of all other comparator medications, see Annex 1.

Exposure assessment windows vary by outcome as shown in Table 9.6. A qualifying exposure can be a medical or pharmacy claim as described in the Exposure Assessment section above. Only the first qualifying UC medication exposure (mirikizumab or comparator medications) in the exposure assessment window will be considered for cohort inclusion.

Table 9.6. Exposure Assessment Windows by Outcome

Outcome	Exposure Assessment Window
Major congenital malformations (MCM)	5 half-lives prior to LMP to End of the First Trimester of Pregnancy
Small for gestational age (SGA)	5 half-lives prior to LMP to EPE
Stillbirth (SB)	5 half-lives prior to LMP to EPE
Preterm birth (PTB)	5 half-lives prior to LMP to <37 Weeks gestation*
Spontaneous abortion (SA)	5 half-lives prior to LMP to <20 Weeks gestation*

Abbreviations: EPE = end-of-pregnancy episode; LMP = last menstrual period.

* The exposure assessment window will extend to the end of the time period indicated (until 36 weeks and 6 days of gestation for PTB, until 19 week and 6 days of gestation for SA) or the EPE, whichever occurs first.

Multiple Exposures:

For the assessment of Objectives 2 and 3, pregnancy episodes cannot have any other cohort-defining medication exposures prior to the first cohort-defining medication. A pregnancy episode cannot qualify for more than one cohort. However, all pregnancy episodes may have other UC biologic medication exposures *after* the first qualifying medication exposure or LMP (if first exposure occurs in the 5 half-lives prior to LMP). For example, if the first cohort-defining medication exposure was for mirikizumab at 10 weeks' gestation and there was a switch to aTNF at 13 weeks' gestation, this pregnancy would be classified in the mirikizumab cohort.

Given that non-biologic medications may be used concomitantly with mirikizumab, aTNF, vedolizumab, and ustekinumab, concurrent exposure to non-biologic medications for UC will be allowed. Non-biologic medications for UC include the following:

- 5- ASA

- Sulfasalazine
- Mesalamine
- Balsalazide
- Olsalazine
- Immunomodulators:
    - Cyclosporine
    - Mercaptopurine
    - Azathioprine
    - Tacrolimus

Methotrexate, leflunomide, ozanimod and etrasimod were excluded from the list of exposures considered for the non-biologics for this study as they have FDA label warnings related to use in pregnancy. Methotrexate and leflunomide are included in the list of potential teratogens in this study.

Finally, a patient with multiple pregnancy episodes will be able to qualify for inclusion in multiple exposure cohorts.

9.3.2. Outcomes

There are 5 outcomes being assessed in this study. MCM is the primary outcome of interest and SGA, SA, SB, and PTB are secondary. SA, SB, and PTB are considered maternal pregnancy outcomes and will be assessed on the mother's claim data, and thus mother-infant linkage will not be required to assess the pregnancy outcomes. MCM and SGA are considered infant outcomes and will be assessed on the infant claims data, and thus mother-infant linkage will be required for proper ascertainment of exposure status and these outcomes. MCM and SGA outcomes will be assessed for all infants that are linked including those born to multiple gestation pregnancies. Each outcome will be analysed separately. A sensitivity analysis will be conducted which assesses infant outcomes of MCM and SGA on both the mother and infant's claims records, irrespective of linkage.

Administrative claims data will be used to identify each outcome on the basis of ICD-10 diagnosis and procedure, CPT/HCPCS, and DRG codes (see Appendices A and K for code lists). The outcomes will be identified utilising validated algorithms (when available) and/or existing best practices from the peer-reviewed literature (for example, EUROCAT for MCMs). See Table 9.7 for more information.

Primary Outcome:

- *Infant Outcome:* MCM
    - MCMs will be defined utilising ICD-10 codes and organ system categories as outlined in EUROCAT (EC 2022). EUROCAT is a European network of population-based registries for the epidemiological surveillance of congenital anomalies. The groupings for MCM are very similar across sources and have been mapped accordingly. EUROCAT outlines ICD-10 diagnosis codes used to identify MCMs in their registries. However, the definitions are not validated. Thus, He et al. (2020) and Palmsten et al. (2014) will supply validated algorithms/logic and EUROCAT will provide the codes for the groupings. A detailed definition of these algorithms and code lists will be provided in the SAP. MCMs classified as genetic syndromes (including chromosomal abnormalities) and positional effects will not be included in the definition of MCM. Additionally, events related to prematurity (e.g., patent ductus arteriosus) will not qualify as an MCM if the infant is born <37 weeks' gestation. These events will count as an MCM if the infant is born ≥37 weeks' gestation. Additional details related to MCM definitions, classifications by organ class, and MCMs excluded due to chromosomal abnormalities, genetic syndromes, positional effects and events related to prematurity will be explained in detail in the SAP. MCMs will be reported in the following ways:
        - Composite MCM (i.e., presence of any MCM)
        - MCMs grouped by organ class using the EUROCAT Clinical Malformation Categories (i.e., presence of at least one MCM in a specified organ class)

Secondary Outcomes:

- *Infant outcome:* SGA
- *Maternal pregnancy outcomes:* SA, SB, PTB

Table 9.7. Outcome Definitions

Outcome	Conceptual Definition	Operational Definition	Validation of the Algorithm
MCM (primary)	Anomalies that affect life expectancy, health status, or physical or social functioning (DeSilva et al. 2016). Overall MCM is the primary outcome; specific malformations and malformations grouped by organ system will be reported	Infants with MCMs will be identified using the validated algorithms developed by He et al. (2020) for non-cardiac malformations and Palmsten et al. (2014) for cardiac malformations present in the infant record anytime from birth through up to 365 days of follow-up. Because these sources used ICD-9 diagnosis and procedure codes, EUROCAT will be utilised for ICD-10 code lists and organ classification schemes. MCM will be assessed among pregnancy episodes with live births and linked infants.	The claims-based algorithm provided by He et al. (2020) had 86% (95% CI, 74%-94%) agreement with physician adjudication for noncardiac congenital malformations. The claims-based algorithm provided by Palmsten et al. (2014) had 77.6% (95% CI: 65.7, 86.2%) agreement with physician adjudication for cardiac malformations.
SA (secondary)	Pregnancy loss before the 20th week (<20 weeks) of pregnancy (Rouse et al. 2017)	Occurrences of medically recognised spontaneous abortions will be identified using the Moll et al. (2021) algorithm (Appendix A), among all pregnancy episodes.	This claims-based algorithm had 100% (95% CI: 93.9%-100.0%) agreement with physician adjudication (Moll et al. 2021).
SB (secondary)	Involuntary foetal loss at 20 weeks of gestation or after (≥20 weeks), or foetus weighing ≥350 g, as recommended by the American College of Obstetricians and Gynecologists (Tavares et al. 2016)	Occurrences of stillbirth will be identified using the Moll et al. (2021) algorithm (Appendix A), among pregnancy episodes with a gestational age of ≥20 weeks.	This claims-based algorithm had 70.8% (95% CI: 50.2%-85.5%) agreement with physician adjudication (Moll et al. 2021).
PTB (secondary)	Live delivery on or after the 22nd week and before the start of the 37th week (≥22 weeks but <37 weeks) of pregnancy (Quinn et al. 2016)	Occurrences of preterm birth will be identified using the Moll et al. (2021) algorithm, among pregnancy episodes with a gestational age of ≥22 weeks and <37 weeks.	This claims-based algorithm has 62.4% (95% CI 52.0%-71.7%) agreement with physician adjudication (Moll et al. 2021).
SGA (secondary)	Infant with birthweight below the 10th percentile for gestational age (Schlaudecker et al. 2017)	Occurrences of SGA will be assessed using the algorithm developed by He et al. (2020). SGA will be assessed among pregnancy episodes with live births and linked infants on the infant record anytime from birth through up to 30 days of follow-up.	The positive predictive value of SGA was 92% (95% CI 82%-97%) (He et al. 2020).

Abbreviations: CI = confidence interval; EUROCAT = European Registration of Congenital Anomalies and Twins; ICD-9/10 = International Classification of Diseases, Ninth/Tenth Revision; MCM = major congenital malformation; PTB = preterm birth; SA = spontaneous abortion; SB = stillbirth; SGA = small for gestational age.

9.3.3. Covariates and Other Variables

The analyses of Objective 3 will account for covariates that are expected to confound the association between medication exposure and each of the outcomes of interest. For a condition to be a confounder, it needs to be associated with the exposure (that is, a predictor of exposure status) and associated with the outcome (that is, a risk factor for the outcome). The analysis will also account for variables associated with the study outcomes only, as inclusion of these variables in the PS model can result in an increase in the precision of the treatment effect without increasing bias (Brookhart et al. 2006).

Table 9.8 presents the relevant covariates considered for inclusion and the time window in which these covariates will be assessed. Covariates assessed prior to the start of the follow-up period were selected for inclusion into propensity score models if they were known risk factors for safety outcomes or identified as potential confounders based on prior literature. The distribution of these variables will be compared across the mirikizumab-exposed and the comparator cohorts before and after application of propensity score methods. Select covariates where the relevant window of assessment continues into or starts during the pregnancy episode and potentially after the initiation of follow-up will be reported descriptively, only.

Variable code lists will be included in the SAP.

Table 9.8. Covariates and Corresponding Assessment Periods

Covariates	Assessment Period
Covariates measured prior to the start of the follow-up period (for consideration in PS models)	
Maternal demographic characteristics	
Age, race/ethnicity, insurance type	LMP
Pregnancy episode start date - calendar dates (year, month)	LMP
Pregnancy/obstetric history (March of Dimes 2018; NIH 2017)	
Number of prior pregnancy episodes, occurrence of prior pregnancy complication (gestational diabetes, placental abruption, placenta previa, preeclampsia/eclampsia, pregnancy with chromosomal abnormality, subchorionic haemorrhage or haematoma, history of preterm birth or incompetent cervix, parity, previous small for gestational age, previous stillbirth, prior caesarean, prior miscarriage), recent pregnancy (less than 180 days between prior birth and LMP, assisted reproductive technology for pregnancy)	All available history until LMP
Exposure timing	
Time to first qualifying exposure after LMP date	From LMP date to the date of the first qualifying drug exposure
Gynaecologic conditions	
Endometriosis or adenomyosis, menorrhagia or dysmenorrhea, urinary tract infection, uterine fibroid, congenital uterine abnormalities	**Starting** 180 days prior to LMP and ending on the start of the follow-up period (exclusive)

Covariates	Assessment Period
Chronic comorbid conditions	
Cardiovascular disease, hypertension, chronic kidney disease, type 1 or 2 diabetes mellitus, hyperlipidaemia, stroke or transient ischaemic attack, thrombophilia (hypercoagulability, prothrombotic state), obesity or overweight, asthma, hypothyroidism, anaemia (any type), malnutrition, sickle cell disease, thyroid disease, HIV infection	Starting 180 days prior to LMP and ending on the start of the follow-up period (exclusive)
Mental health	
Anxiety disorder, bipolar disorder, depression, post-traumatic stress disorder	Starting 180 days prior to LMP and ending on the start of the follow-up period (exclusive)
Other autoimmune disease	
Rheumatoid arthritis, psoriasis, Crohn's disease, ankylosing spondylitis, hidradenitis suppurativa, uveitis, systemic lupus erythematosus, Hashimoto's disease, celiac disease, scleroderma, psoriatic arthritis, Sjögren's disease, Grave's disease, Addison's disease, dermatomyositis, myasthenia gravis, Type 1 diabetes mellitus	All available history until the start of the follow-up period (exclusive)
Substance use	
Tobacco use, alcohol abuse or dependence, drug abuse or dependence	All available history until the start of the follow-up period (exclusive)
Infections	
Toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis, varicella, parvovirus B19, Zika virus, LCMV, influenza, chlamydia, human papillomavirus, gonorrhoea, HIV, trichomoniasis, COVID-19, maternal sepsis, bacteraemia, chorioamnionitis, pneumonia, listeriosis	Starting 180 days prior to LMP and ending on the start of the follow-up period (exclusive)
Other indications for mAbs (Puthenpurail et al. 2021)	
Cancer (any type), organ transplant, multiple sclerosis, juvenile idiopathic arthritis, giant cell arteritis, cytokine release syndrome, psoriasis, uveitis, osteoporosis, vasculitis	All available history until the start of the follow-up period (exclusive)
UC medication exposures (excluding steroids)	
Number of prior unique UC medications aTNF: infliximab, adalimumab, golimumab, mirikizumab JAKi: tofacitinib, upadacitinib Vedolizumab Ustekinumab Non-biologics: sulfasalazine, mesalamine, balsalazide, olsalazine, methotrexate, leflunomide, cyclosporine, mercaptopurine, azathioprine, tacrolimus, ozanimod, etrasimod	All available history until the start of the follow-up period (exclusive)
Steroid exposure (oral, intravenous, rectal)	
Budesonide, methylprednisolone, prednisolone, prednisone	Starting 180 days prior to LMP and ending on the start of the follow-up period (exclusive)
Vaccine exposures	
Influenza; Tdap; hepatitis A; hepatitis B, human papillomavirus; measles; mumps; rubella; meningococcal, pneumococcal, varicella, COVID-19	Starting 90 days prior to LMP and ending on the start of the follow-up period (exclusive)

Covariates	Assessment Period
UC-related healthcare utilisation	
Number of UC-related hospitalisations, number of UC-related ED visits	Starting 180 days prior to LMP and ending on the start of the follow-up period (exclusive)
Covariates measured after the start of follow-up (reported descriptively only)	
Infant demographic	
Infant sex (among infants linked to mother)	At first recorded claim on or after birth on the infant's record
Obstetrical conditions (March of Dimes 2018; NIH 2017)	
Multifoetal gestation, gestational diabetes, intrauterine device in place during pregnancy, placental abruption, placenta previa, preeclampsia and eclampsia, pregnancy with chromosomal abnormality, incompetent cervix, assisted reproductive technology for pregnancy, subchorionic haemorrhage or haematoma, vaginal bleeding	LMP until pregnancy outcome (any time during the pregnancy episode)
Healthcare utilisation during pregnancy	
Number of prenatal visits, number of prenatal tests performed	LMP until pregnancy outcome (any time during the pregnancy episode)
Exposure to nonbiologic medications during an observed pregnancy episode	
Nonbiologic medication exposure for mirikizumab, aTNF, vedolizumab, and ustekinumab-exposed pregnancy episodes	LMP until pregnancy outcome (any time during the pregnancy episode)
Infections	
Toxoplasmosis, Rubella, Cytomegalovirus, Herpes, Syphilis, Varicella, Parvovirus B19, Zika virus, LCMV, influenza, chlamydia, human papillomavirus, gonorrhoea, HIV, trichomoniasis, COVID-19, maternal sepsis, bacteraemia, chorioamnionitis, pneumonia, listeriosis	LMP until pregnancy outcome (any time during the pregnancy episode)
UC subtypes	
Proctitis, left-sided colitis, or extensive colitis	All available history until exposure to mirikizumab or comparator medication

Abbreviations: aTNF = anti-tumour necrosis factor; COVID-19 = coronavirus disease 2019; ED = emergency department; HIV = human immunodeficiency virus; JAKi = Janus kinase inhibitor; LCMV = lymphocytic choriomeningitis virus; LMP = last menstrual period; mAb = monoclonal antibodies; PS = propensity scores; Tdap = tetanus, diphtheria, and acellular pertussis; UC = ulcerative colitis.

9.4. Data Sources

All analyses will use patient-level claims data from the HealthVerity MOM. HealthVerity MOM was selected as the optimal fit-for-purpose data source for the research questions following the application of a structured process to identify fit-for-purpose data (Gatto et al. 2019). The underlying source of the MOM dataset is known as "Source 20" or "PS20", and is a large, national, closed claims dataset that includes Commercial, Medicaid, and Medicare Advantage payers across the US. The entire MOM dataset contains information on nearly 2 million pregnant

women 10-60 years of age. A subset of the pregnancy episodes with live births have linked infant records with an overall linkage rate of 47.2%, providing the opportunity to evaluate infant outcomes (MCM and SGA) in this linked subgroup. The actual linkage rate may change when all of the patient selection criteria have been applied for this study. Pregnancy outcomes (SB, PTB, and SA) do not require a linked infant and will thus be evaluated among all pregnancies that qualify for the respective cohorts, irrespective of infant linkage. The HealthVerity MOM dataset has the ability to identify diagnoses in both mother and linked infant with an average follow-up of 2 years for the linked infant.

PS20 sends a unique linking file to HealthVerity that contains supplier-specific patient identifiers relating pregnancy episodes with a live birth to infants in the database. To generate a mother-infant linkage PS20 requires the mother and infants to meet all of the criteria below:

- at least one medical claim with activity of interest in the mother's records (pregnancy-related and/or delivery)
- at least one medical claim in the infant's records occurring within 30 days of the mother's pregnancy-related claim
- mothers must be age ≥14 years and female sex, and
- infants must be age ≤1 year

Linkage is performed with a shared subscriber key for Commercial insured patients, or the last name and street address match for patients insured via Medicaid and not already linked via subscriber key. The HealthVerity MOM linking process is similar to that used by select FDA Sentinel Data Providers as described in the Mother-Infant Linkage FAQs published by the FDA Sentinel Operations Center (FDA 2019).

Data elements for both mother and infant include demographics, observability, medications prescribed and administered, clinical and inpatient stay administrative data, and coded diagnoses and procedures. Additionally, the HealthVerity MOM dataset contains information on maternal medication including dose and timing. The data range of the overall dataset currently spans 01 January 2008 to July 2023 (mother-infant linkage is available starting from 01 January 2018). Use of data and the granularity available is controlled by HIPAA requirements or application of public health exemption. No PHI or PII leaves the data owner's possession, and all research data are certified HIPAA compliant by expert determination.

Preliminary explorations of missingness of demographic variables performed among all patients in the entire HealthVerity MOM dataset prior to the initiation of this study identified: <1% mothers with missing age, 42.7% mothers with missing race, <1% mothers with missing insurance, and 5% linked pregnancies with missing infant sex. Estimates of missing data are based on the dataset spanning 01 January 2008 to 07 October 2022. Estimates are subject to change pending receipt of final dataset.

In claims databases, absence of recorded data by healthcare professionals is not expected for the exposures, outcomes, concomitant medications, and comorbidities in the current study. That is, the presence of a claims record for a disease diagnosis, for instance, assumes the condition is present, while absence of such a record assumes the patient does not have the condition. This also assumes that all clinically significant events are coded in the claims and that there are no missing data for the presence of a comorbid condition or medications used in this study. If there is under-recording, some misclassification of patient status for these variables may occur.

9.5. Study Size

The required sample size is calculated for the primary outcome of any MCM among liveborns. Sample size calculations assume a prevalence of 3% in all comparator groups; this is consistent with background risks in the general population (CDC 2008; Clowse et al. 2016; Mahadevan et al. 2018). The sample size was calculated to find a minimum detectable relative risk of at least 2.5, with a 2-sided probability of type 1 error (alpha) of 5%, and 80% power.

With these assumptions, 368 mirikizumab-exposed mother-infant linked pregnancy episodes and 368 mother-infant linked pregnancy episodes in each of the comparator groups of interest will be targeted for the MCM composite outcome.

Sample sizes for varying assumptions are presented in Table 9.9. The power required for the other study outcomes is estimated based on the number of pregnancy episodes required for the primary outcome of MCM and estimated prevalence of these outcomes in the mirikizumab-exposed and comparator medication-exposed pregnancy episodes.

Table 9.9. Required Sample Size to Assess Major Congenital Malformations and Estimated Statistical Power to Assess Other Study Outcomes

Outcome	Minimum detectable Relative Risk (RR) and Assumed Prevalence	Sample Size	Calculated Power
Required sample size to assess MCM with 80% power			
MCM	RR = 3.0 and MCM prevalence of 3% in comparator cohorts	231 mirikizumab- exposed pregnancy episodes and 231 comparator group pregnancy episodes	Given (80%)
MCM	RR = 2.5 and MCM prevalence of 3% in comparator cohorts	368 mirikizumab- exposed pregnancy episodes and 368 comparator group pregnancy episodes	Given (80%)
MCM	RR = 2.0 and MCM prevalence of 3% in comparator cohorts	729 mirikizumab- exposed pregnancy episodes and 729 comparator group pregnancy episodes	Given (80%)
Estimated power for other study outcomes given required sample size for MCM			
SGA	RR = 2.5 SGA prevalence of 9% in comparator cohorts (Martin et al. 2018)	368 mirikizumab- exposed pregnancy episodes and 368 comparator group pregnancy episodes (given)	>90%
Stillbirth	RR = 2.5 Stillbirth prevalence of 0.6% in comparator cohorts (Say et al. 2006)	368 mirikizumab- exposed pregnancy episodes and 368 comparator group pregnancy episodes (given)	24%

Outcome	Minimum detectable Relative Risk (RR) and Assumed Prevalence	Sample Size	Calculated Power
Spontaneous abortion	RR = 2.5 Spontaneous abortion prevalence of 20% in comparator cohorts (Rossen et al. 2018)	368 mirikizumab- exposed pregnancies and 368 comparator group pregnancy episodes (given)	>90%
Preterm birth	RR = 2.5 Preterm birth prevalence of 10% in comparator cohorts (Martin et al. 2019)	368 mirikizumab- exposed pregnancies and 368 comparator group pregnancy episodes (given)	>90%

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

9.5.1. Feasibility of Obtaining Sample Size for Objective 3

The available number of pregnancies exposed to mirikizumab will depend on:

- uptake of mirikizumab among US women of childbearing age
- whether the women become pregnant while exposed to mirikizumab
- whether the data source selected will capture sufficient pregnancies exposed to the medications of interest
- whether the women remain enrolled in the data source for sufficient time to be followed to the end of pregnancy and meet study inclusion/exclusion criteria (relevant for pregnancy outcomes of spontaneous abortions, stillbirth, and preterm birth), and
- whether the infant can be linked to the exposed mother (relevant for infant outcomes of MCM and SGA).

Uptake of mirikizumab among women of childbearing age in the US could not be estimated given that mirikizumab has not yet been introduced to the US market at the time of the writing of this protocol.

Current evidence indicates that the use of biologics during pregnancy among patients with IBD (UC and CD) is very limited. For example, in a secondary database study using US (Optum and Medicaid analytic extract databases) as well as EU (the Swedish National registers) databases, exposure to biologic medications during pregnancy among 7907 patients with IBD was found to be limited to only aTNFs (Broms et al. 2021). No women were found to be exposed to other biologics that are indicated for the treatment of IBD, such as vedolizumab or ustekinumab (Broms et al. 2021). In addition, exposure during pregnancy to aTNFs among women with CD or UC was found to be very limited in both the US, as well as in Swedish national registers (Broms et al 2021). Of the patients using aTNFs at baseline, only 55.8% continued use during the pregnancy in Optum data from the US and only 11.8% continued in Sweden. Results also showed that aTNFs were less often initiated during pregnancy (Broms et al. 2021).

Taking into consideration the limited biologic exposures during pregnancy among patients with UC together with reliance of sample size on market uptake, the minimum detectable target RR of

at least 2.5, and the resulting target sample size for the composite MCM outcome presented in Section 9.5, provide a potentially realistic sample size estimation.

9.6. Data Management

This study is being conducted by a third party, Aetion. The datasets and analytic programs will be stored according to the vendor's procedures.

When data is received at Aetion from a vendor, the Data Operations team creates a templated data ingestion ticket and tags all responsible team members. Details of the ingestion ticket include the location where the data was uploaded, the location where the data should be transferred, and the date and time of the upload. All data is retained and stored by client, dataset, and revision.

The schema of the data received is compared to the expected schema per vendor documentation for new data sets and to previously received data for data updates to identify missing variables or new variables. Event density distributions are created for new data sets and data updates in order to explore event data over time and identify possible gaps or missing files. For some frequently received data, lists of files received are compared between data updates in order to identify files that have been added or unexpectedly dropped.

As part of the data review process, raw data review is routinely conducted to understand contents of the database and scientific integrity checks are performed to ensure the contents of the data are consistent with the expected data quality as laid out in the applicable data usage agreement. Some of the key characteristics explored in this process include:

- table structure (number of rows, columns, column names, etc.)
- summary counts per table (i.e., non-missing counts, unique counts)
- variable distribution (e.g., min, mean, median, max for numeric variables; top frequencies for categorical variables)
- date range (min, max and distribution over a time period), and
- missingness percentage of attributes.

All code is version-controlled and stored in GitHub by dataset, client, and revision. All raw data, code, transformed data, metadata, and validation reports are stored in a client-specific bucket and organised by dataset and revision in a structured folder system. The code and data used for a particular data connection or data update can be accessed at any time by users of the Data Integration and Engineering teams with appropriate permissions.

9.7. Data Analysis

9.7.1. Descriptive Analysis for Objective 1

The purpose of Objective 1 is to monitor the use of mirikizumab during pregnancy by describing the demographic and clinical characteristics of pregnant women who are exposed to mirikizumab. All pregnancies that meet the mirikizumab cohort definitions will be included in the analysis of Objective 1. An attrition table will be provided to demonstrate the impact of each inclusion/exclusion criteria on the identification of the cohort. Dichotomous and categorical

covariates will be summarised using counts with percentages, and non-missing values of continuous variables will be summarised using means with SD, medians with IQR, as well as N, N missing, minimum and maximum. Missing data will be quantified in terms of the number of unique pregnancies or infants (depending on the covariate) with missing data, but data will not be imputed.

9.7.2. Descriptive Analysis for Objective 2

The purpose of Objective 2 is to describe the occurrence of adverse pregnancy and infant outcomes of interest among women with UC (and infants linked to these women) who are exposed during pregnancy to mirikizumab, aTNFs, and vedolizumab medications during pregnancy. The analysis will be conducted at the level of pregnancy episodes. Therefore, for women with more than one exposed pregnancy episode during the study period, each episode meeting the cohort inclusion/exclusion criteria will be included for analysis. Further detail regarding multiple exposed pregnancies is described in Section 9.3.1.

All pregnancy episodes, and linked infants (when available), that meet the all mirikizumab cohort, mirikizumab UC cohort, all comparator UC cohorts, and outcome-specific requirement definitions will be included in the analysis of Objective 2. An attrition table will be provided to demonstrate the impact of each inclusion/exclusion criteria on the identification of the corresponding cohort.

Descriptive analyses of all study outcomes will be conducted in mirikizumab-exposed and comparator group pregnancies. Counts of outcomes will be presented, along with trimester of exposure to mirikizumab or the comparator medications for those with the event. The prevalence of each outcome will be reported as count per 100 pregnancies or live births along with the 95% CI. The denominator (i.e., pregnancies at risk for a particular outcome of interest) varies between outcomes. Outcome-specific denominators are summarised in Table 9.10.

Additionally, given that a variable amount of follow-up may be available after birth for infants in the outcome assessment for MCM, the following incidence rate will be calculated: # of infants with MCM event / total days in infant outcome follow-up assessment period) / 365 * 1000. MCM rate results will be reported as a composite outcome (i.e., any MCM event) and by organ class using the EUROCAT categories (i.e., presence of at least one MCM in a specific organ class).

Table 9.10. Denominators for Calculation of Outcome Prevalence for Objective 2

Outcome	Primary Analysis Denominator
MCM	Pregnancies ending in live births with linked infant data that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.
SGA	Pregnancies ending in live births with linked infant data that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.
Stillbirth	Pregnancies with a gestational age of ≥20 weeks that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.
Preterm Birth	Pregnancies ending in a live birth with a gestational age ≥22 weeks with first qualifying exposure occurring <37 weeks' gestation that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.

Spontaneous Abortion	All pregnancies with first qualifying exposure occurring on or prior to 20 weeks' gestation and that meet the cohort and outcome-specific patient selection criteria in Section 9.2.1 and Table 9.4.

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

In addition to the analysis described above, a descriptive analysis will be conducted to assess the magnitude of differences between pregnancies with a linked infant and pregnancies without a linked infant. The purpose of this analysis is to understand the comparability of pregnancies in the HealthVerity MOM dataset that contribute to linked infant data for infant outcome assessment and to provide context for any potential selection bias associated with linkage of mothers to infants.

Variables in Table 9.8 that are assessed prior to the start of the follow-up period (i.e., maternal demographic characteristics, obstetrical history, chronic comorbid conditions, etc.) will be compared between pregnancies with a linked infant and pregnancies without linked infants. This will be done for each of the four primary cohorts of interest for Objective 2 for pregnancies meeting the criteria for the MCM and SGA analysis (see Table 9.4). Dichotomous and categorical variables will be summarised using counts with percentages, and non-missing values of continuous variables will be summarised using means with SD and medians with IQR. Categorical and continuous covariates will be compared using chi square and t-tests, respectively. If categorical variables have levels with expected counts of <5 events, the Fisher's exact test will be used. If continuous covariates are non-normally distributed, the Wilcoxon rank sum test will be used.

Stratified analyses for Objective 2

Analyses will be stratified by timing of first exposure by first, second and third trimesters. Pregnancies for which first exposure occurs prior to LMP or during the first trimester will be classified as first trimester. Time periods defining trimesters can be found in Section 9.2.1.3.

9.7.3. Comparative Analysis for Objective 3

Objective 3 will be analysed if there is sufficient sample size of mirikizumab and comparator-group exposed pregnancies for pregnancy outcomes, and sufficient number of women with linked infants for infant outcomes. The exposed cohort of interest for comparative analyses is the UC cohort with exposure to mirikizumab. The three primary comparator cohorts will consist of pregnancies with UC with exposure to aTNFs, vedolizumab, or ustekinumab, during the pregnancy episode. See Section 9.2.1.2 for further information on cohorts.

9.7.3.1. Propensity Score Applied in Comparative Analyses

Medication exposure in non-interventional studies does not occur at random and is a result of patient, physician, and system-related factors. When these factors are associated with the outcome of interest, comparisons of treatment exposure cohorts to comparator cohorts (either comparator cohort treated with another other drug or an unexposed cohort) will be confounded due to channelling bias. Propensity scores can address this imbalance by providing a mechanism to compare patients with concordant baseline risk but discordant exposure (Schneeweiss 2007). For clarity, covariates included in the propensity score models are also referred to as confounders because they confound the association between exposure and outcome.

A propensity score is an estimate of the probability that a patient receives a particular treatment, conditional on measured characteristics at the time a treatment decision is made (Rosenbaum and Rubin 1983). For this study, a patient's propensity score will reflect the predicted probability of exposure to mirikizumab versus a comparator medication/group during a qualifying pregnancy episode given a set of measured confounders. In this study design, variables considered for inclusion in the PS model will be assessed in varying time periods (see Table 9.8) prior to LMP and up to the start of the follow-up period for all cohorts.

PS will be estimated with multivariable logistic regression models predicting the probability of being exposed to mirikizumab versus comparator medications (i.e., separate models predicting the probability of exposure during the exposure assessment window to mirikizumab versus aTNF, mirikizumab versus vedolizumab, and mirikizumab versus ustekinumab) during pregnancy (dependent variable) conditional on measured covariates (independent variables). The outcome variable in the PS model is exposure to medication (mirikizumab during pregnancy, while covariates identified *a priori* as potential confounders are included as independent variables and are assessed in the 180 days prior to LMP up to the date of the first qualifying exposure. Table 9.8 presents the relevant covariates considered for inclusion and the time window in which these covariates will be assessed.

Covariates assessed prior to the start of the follow-up period were selected for inclusion into PS models if they were known risk factors for safety outcomes or identified as potential confounders based on prior literature. The distribution of variables in Table 9.8 will be compared across the mirikizumab-exposed and the comparator cohorts before and after application of propensity score methods. Balance will be assessed using the standardised mean difference. An ASD >0.2 will indicate substantial imbalances between the groups. Additionally, because patients may have varying amounts of time during which their baseline characteristics are assessed, time between LMP and date of first qualifying exposure will be used as a variable in the propensity score model.

Combining or eliminating PS model covariates may occur to minimise the risk of model overfitting and non-positivity if the number of included covariates exceeds the recommended "rule of thumb" of having ≥10 exposed pregnancies per covariate (Schuster et al. 2016). If the ratio of exposed pregnancies to PS model covariates is <10:1, determination of which covariates to combine or exclude will occur in collaboration with clinical and statistical experts. Decisions to exclude covariates will prioritise those with minimal confirmatory published evidence for their association with the specific study outcome.

Select covariates where the relevant window of assessment continues into or starts during the pregnancy episode and potentially after the initiation of follow-up will be reported descriptively, only.

Trimming, matching, stratification, and weighting on the propensity score are commonly applied techniques for using the propensity to adjust for confounding. However, the matching process may result in a high number of unmatched patients and stratification may result in strata with few or no patients.

As such, inverse probability of treatment weighting (Austin and Stuart 2015) will be the preferred application of PS adjustment in order to minimise sample size loss from other methods such as stratifying and matching methods. This PS application approach will weight exposed and

referent patients on the inverse probability of receiving the treatment they actually received, conditional on observed covariates included as independent variables in the PS model. IPTW will be calculated as 1/PS among patients exposed to mirikizumab and as 1/(1-PS) among the comparator group. Weighting the outcome model by the IPTW results in a pseudo-population twice as large as the original population in which every patient appears as a treated and untreated patient (Hernán and Robins 2020). Patients with a high probability of receiving treatment are assigned a smaller weight and patients with a low probability of receiving treatment are assigned a larger weight. The resulting effect estimate when utilising IPTW will estimate the ATE in the population. This estimand provides the ATE assuming that every patient in the study population would be observed under assignment of treatment and under assignment of no treatment. Additional details on IPTW implementation will be provided in the SAP.

Balance will be assessed for each covariate prior to and after IPTW with the ASD. An ASD $\leq$0.1 will indicate acceptable balance between the groups. Variables with a small residual imbalance (0.10 $\leq$ASD $\leq$0.20) may be considered acceptable to retain if the difference is not deemed clinically meaningful between the populations of interest by clinical experts. Factors considered for inclusion in the estimation of PS are measured during the baseline covariate assessment period and are presented in Table 9.8.

Covariates that are not sufficiently balanced between groups (with ASD >0.20) will be considered for inclusion as covariates for regression adjustment in the final outcome models.

9.7.3.2. Statistical Analysis for Objective 3

Given that all pregnancies will be required to have one of the study outcomes and continuous enrolment throughout the entirety of the pregnancy episode, there will be no censoring due to loss to follow-up, death, or disenrollment. Accordingly, the relative risk will be the effect estimate reported in comparative analyses for Objective 3. Crude and propensity score-adjusted relative risks (95% CI) will be estimated for each outcome by robust (modified) Poisson regression using a log link and a Poisson distribution without an offset parameter (Zou 2004). For MCM, the primary analysis will consider only exposure in the first trimester.

Given the safety-related objectives of the study, a more conservative approach will be used (i.e., retain the significance level of 0.05 to avoid missing a safety signal) and no adjustments will be made for multiple comparisons.

Analyses will account for intra-subject correlation due to the inclusion of multiple pregnancies for a given woman by employing robust standard errors when calculating all p-values.
A bootstrap variance estimator will be used in all outcome models to account for the fact that weights are estimated rather than precisely known for intra-subject correlation occurring when multiple pregnancy episodes per mother are included. Simulations show that this approach results in the least bias with respect to estimation of standard errors and provides confidence intervals with correct coverage rates relative to both a naïve model-based variance estimator and a robust sandwich-type variance estimator (Austin 2016). A robust sandwich-type variance estimator will be used as a sensitivity analysis (see Section 9.7.3.3).

Stratified analyses for Objective 3

Comparative analyses of Objective 3 will be performed in the case that there is sufficient sample size (sufficient mirikizumab and comparator group exposed pregnancies for pregnancy

outcomes, and sufficient number of women with linked infants for infant outcomes) and balance between groups. Analyses will be stratified by timing of first exposure by first, second and third trimesters. Pregnancies for which the first exposure occurs prior to LMP will be classified as first trimester. Time periods defining trimesters can be found in Section 9.2.1.3. Propensity scores will be re-estimated within each subgroup given sufficient sample size, and IPTW will be implemented within subgroups. More details regarding subgroup analysis will be provided in the SAP.

9.7.3.3. Sensitivity Analysis

The following sensitivity analyses will be executed to test the robustness of the comparative analyses for the primary outcome, MCM, unless otherwise specified. These analyses will be executed as allowable by sample sizes and will be executed independently of each other. Should any of the below described analyses suggest the primary analytic approach was sensitive to study specifications, the sensitivity analysis approach will be extended to other outcomes as well. Details related to the implementation of these sensitivity analysis will be provided in the SAP.

- **MCM Outcomes:** In the primary analysis for MCM, only malformations recorded on infant claims among pregnancies with linked infants are included in the outcome definition. A sensitivity analysis will be conducted among all pregnancies meeting the inclusion/exclusion criteria for the MCM cohorts, regardless of infant linkage status. For MCM, malformations recorded on the mother's claims during the pregnancy will also be counted as an infant malformation assuming it is not designated as a malformation in the mother. MCMs observed in the mother's claims only are required to occur during the pregnancy episode but may not occur within the time period starting 90 days prior to LMP date through 105 days after LMP date (He et. al. 2020).
- **SGA Outcomes:** In the primary analysis for SGA, only diagnoses recorded on infant claims among pregnancies with linked infants are included in the outcome definition. A sensitivity analysis will be conducted among all pregnancies meeting the inclusion/exclusion criteria for the SGA cohorts, regardless of infant linkage status. For SGA, indication of SGA on the mothers' claims during the pregnancy will count as an SGA outcome (He et. al. 2020).
- **Misclassification of UC:** Given that UC and CD may present with similar symptoms and are both classified as IBD, some claims algorithms for UC and/or CD exclude patients with diagnosis of both UC and CD to reduce disease misclassification (McAuliffe et al. 2015). Recognizing the potential for misclassification of UC, a sensitivity analysis will be conducted where patients with a claim for both UC and CD in the 180 days prior to LMP until the first exposure to mirikizumab or comparator group will be excluded from the study.
- **Teratogen use:** In the primary analyses of all outcomes, pregnancies will be excluded if they are exposed to teratogens within 5 half-lives of the respective teratogen prior to the LMP or any time from the LMP date until the first qualifying exposure to mirikizumab or comparator medication. A sensitivity analysis will be conducted that also excludes pregnancy episodes with exposure to teratogens after the first qualifying exposure to mirikizumab or comparator medication, but within the relevant outcome assessment window. For a list of examples of potential teratogens and their half-lives, see Appendix D.

- **Multiple medication exposures:** In the primary analyses (observational analogue of ITT approach), exposure to other UC medications after the start of follow-up for each respective medication is allowed, meaning that patients may have exposure to both mirikizumab and a comparator medication. A sensitivity analysis (observational analogue of PP approach) will be performed where pregnancy episodes with exposure to other biologic UC medications after the first qualifying medication exposure for a given cohort will be excluded (i.e., the outcome assessment window will end prior to the other biologic exposure) for the assessment of Objectives 2 and 3.
- **Non-biologic UC cohort:** Given that non-biologic drugs are typically used prior to medication with and/or concomitantly with mirikizumab or other biologic drugs for UC, a sensitivity analysis will be conducted among a cohort of pregnancy episodes with use of only non-biologic medications (i.e., no mirikizumab or comparator medications). This group may provide additional contextualization of the risk of pregnancy safety outcomes. Further details regarding the inclusion and exclusion criteria for this cohort will be provided in the SAP.
- **Expand medication exposure windows:** A sensitivity analysis will be performed modifying the exposure assessment window in the mirikizumab and all comparator cohorts for MCM outcomes. While the primary analysis analyses qualifying exposures during the first trimester, this sensitivity analysis will analyse exposures across the entire pregnancy episode.
- **Assessing sensitivity to propensity score method:** In addition to the IPTW used in the comparative analysis of MCM, PS matching will be used as a sensitivity analysis to test robustness of results to statistical model specifications. The PS matching will be done at a 1:5 fixed ratio using nearest-neighbour matching without replacement with a calliper of 1%. PS matching will be performed at the pregnancy level among pregnancies with linked infant data satisfying the inclusion and exclusion criteria for MCM outcome analysis. The performance of the PS modelling and matching procedure will be assessed through visual evaluation of the PS estimate distribution kernel density plots pre- and post-matching. In the event of sample loss following PS matching resulting in insufficient statistical power, increasing the calliper in 1% increments (up to 5%) may be considered.
- **Case verification**: for outcomes where no validated algorithm is available by the time of the final report, case verification will be initiated. This will be accomplished through linking the claims data to electronic health record data for clinical review and verification of the specific outcome. Sensitivity analyses will assess robustness of results to only include verified cases utilising the EHR portion of the HealthVerity data (more details to be provided in SAP).
- **Variance estimation:** For the analysis of Objective 3, the sandwich variance estimator will be used as an alternative variance adjustment method to account for the fact that weights are estimated rather than precisely known for intra-subject correlation occurring when multiple pregnancy episodes per mother are included.

- **Mediator effects:** To avoid adjusting for a covariate that may act as a mediator between the exposure and outcome (i.e., the qualifying exposure increases the risk of the covariate, which in turn, increases the risk of the outcome), two sensitivity analyses will be conducted
    - Reduced model: Specifically, for the analysis of Objective 3, the set of covariates used to estimate PS will be limited to those which the researchers believe cannot be influenced by the use of mirikizumab (e.g. age, race/ethnicity, insurance type, pregnancy episode start date).
    - Restrict exposure to first in data: For Objective 3, a washout period will be applied to ensure that pregnancy episodes will be restricted to those in which the first mirikizumab or comparator medication exposure occurring during the pregnancy episode (i.e., on the LMP date or during the pregnancy) is the first observable exposure in all available data. This analysis will only be feasible if sufficient sample size is met for a comparative analysis, as described in Section 9.5.

9.7.3.4. Interim Analysis

An interim analysis report will be submitted to the EMA within four years after the start of data collection. This analysis will include an execution of descriptive analysis for the primary objective only, as described in Sections 9.7.1 and 9.7.2.

Comparative analyses will not be executed for this interim analysis unless the target sample size is met and PS methods are performed.

9.8. Quality Control

Aetion will build measures for cohort identification, outcomes and covariates based on codes and algorithms described in this protocol. Further details about definitions for all variables to be used in the study, including code lists, will be included in the SAP. All measures created will undergo independent quality control review by at least one additional analyst or scientist under the supervision of the Study Lead.

This protocol will be strictly followed when conducting the analysis of this study. All cohorts developed, statistical analyses implemented, and tables completed will undergo quality control review by at least one additional analyst or scientist under the supervision of the Study Lead. The Study Lead will review all results tables and other final deliverables to confirm accuracy, logical flow, and appropriate format.

This secondary data collection study follows the Guidelines for GEP laid out in 2005 FDA GPP (FDA 2005), Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets (FDA 2013) and the 2015 ISPE GPP (ISPE 2015). For EU PASS studies, include reference to The ENCePP Guide on Methodological Standards in Pharmacoepidemiology (ENCePP 2010).

9.9. Strengths and Limitations of the Research Methods

Strengths of this study

Real-world data from the HealthVerity MOM database in the US are generated during routine clinical care and are representative of the underlying populations. Claims data sources present a perspective of evidence outside of the tightly controlled conditions of RCT and reflect the sociodemographic characteristics of the moderate-to-severe UC population. Claims data may contain more information on baseline patient health and healthcare utilisation (i.e., visits, medications used, hospitalisations) relative to registry and clinical trial data because claims do not rely on patient recall and report.

Potential limitations of this study

Data source
This study is reliant on an analysis of administrative insurance claims data. Use of administrative claims data offers many strengths for pharmacoepidemiology research, including a large source population and the availability of comprehensive data across the spectrum of patient care (e.g., inpatient and outpatient care). However, all analyses reliant on administrative claims data have limitations, given the primary reason for collecting the data is for billing and reimbursement purposes and not specifically for research purposes.

Because this study is conducted among women with health insurance in the US, generalisability of the study results beyond that source population is not known. Thus, mothers' medical history prior to pregnancy may be limited depending on how long they are observable in the dataset. Further, mothers who disenroll from the database prior to the end of the pregnancy will not be included in the study because the validated algorithm to determine the start and end of the pregnancy relies on knowing the pregnancy outcome. In addition, some mothers may disenroll after the infant is born but prior to the end of maximum infant follow-up (12 months). This will likely result in the infant being disenrolled, the infant follow-up ending, and the potential for missed MCM diagnoses that are diagnosed later in infancy.

The study relies on the linkage of mothers to their infants in the administrative claims data in order to be able to assess infant outcomes. The inability to link infants to mothers is largely a function of infants not remaining on their mother's insurance plan (e.g., infant switches to the father's insurance plan). If there is any unanticipated systematic bias related to study outcomes in those infants who are unable to be linked, the outcome estimates may be biased. A descriptive analysis will be conducted to assess the degree of differences in baseline characteristics for the linked and unlinked pregnancies. In addition, if the linkage rate in the study population is substantially lower than anticipated it will take longer to reach the desired sample size for adequate study power for analysis related to infant outcomes for Objective 3.

Medications or vitamins purchased OTC, and illicit drug use are not routinely recorded in the source data. However, prescription vitamin use, as well as OTC drugs received with a prescription (e.g., acetaminophen), are recorded, as are codes for drug misuse and abuse. OTC medications that may be used in the UC population (e.g., NSAIDs or antidiarrhoeals) are not expected to be strong confounders as they are not likely related to outcomes of interest under normal use conditions. Thus, missing information on OTC medications is expected to have negligible impact on the study.

Data about exposure to tobacco smoke, consumption of alcohol, and abuse/dependence on drugs are thought to be important confounders for this research question. The ascertainment of these variables is limited to diagnosis codes and filled prescriptions for medication used to aid in cessation of smoking and is known to be an underestimate of the population who smokes and consumes alcohol.

Identification of pregnancy episodes

Pregnancy milestones, such as LMP, gestational age, start and end of trimesters, and pregnancy and infant outcomes, are estimated using medical and pharmacy claims. While the study utilises a validated algorithm to identify these milestones, they may under or overestimate the true timing of these events.

Patient diagnosis and patient characteristics

Patients included in Objectives 2 and 3 in the current study are required to have at least one diagnosis claim for UC. This may result in patients who do not truly have UC being included in the study, as it has been shown that selecting patients based on just a single diagnosis record can be associated with poor PPV (Abdalla et al. 2021; Hsu et al. 2017). However, this study requires pregnancies to have at least one prescription claim for mirikizumab or a comparator medication, which is thought to increase the positive predictive value, as the use of these drugs would affirm presence of UC. Additionally, a sensitivity analysis will also be performed that includes excluding patients with a diagnosis code for CD, which will help to understand the robustness of the UC diagnosis inclusion criterion in the primary analysis.

Additionally, UC severity cannot be reliably captured using insurance claims data. Several of the medications of interest (mirikizumab, TNFi and vedolizumab) are indicated for moderately to severely active UC. However, non-biologic medications may be used to treat the general UC population, which may result in mirikizumab-treated pregnancies compared to a less severe population for the assessment of study outcomes. The consideration of number of hospitalizations, emergency room visits, and use of steroids in the baseline period, which can all be proxies for UC severity, in the calculation of the propensity score can help balance mirikizumab and non-biologic medication-exposed pregnancies on severity level.

Age is recorded in the HealthVerity MOM database as a categorical variable that uses 5-year age bands. In order to be in compliance with HIPAA, it is not possible in this study to determine exact age at time of pregnancy outcome. This will only impact the results if the risk of adverse pregnancy outcome varies by age increments less than 5 years.

Target trial emulation design in observational data

The target trial emulation framework can prevent certain biases in observational analyses, including immortal time bias that could result from a failure to align eligibility, treatment assignment, and start of follow-up while also identifying situations where adequate emulation may not be possible using the data at hand. In order to align these 3 parameters and limit the related potential immortal time bias, this study will use the target trial emulation framework that has been adapted for examining pregnancy related exposure and outcomes in observational secondary database studies by Hernández-Díaz et al. (2023).

However, some limitations may persist in observational studies regardless of study design. Among these are bias due to missing data, residual confounding, and misclassification of

exposures and outcomes. Specifically, a limitation relating to the observational analogue of the ITT approach used in the primary analysis of this study, is that patients may be exposed to more than one UC medication during the follow-up period, posing challenges in estimating the independent effect of the study medications on study outcomes. Depending on the true, unknown effect of these medications on study outcomes, this approach may result in biased estimates, and this bias could be towards or away from the null. For example, in the case that the true effect of mirikizumab is an increase in risk of study outcomes relative to comparator medications, the current study approach may result in estimates that are biased towards the null, underestimating the relative risk of safety outcomes for mirikizumab. A sensitivity analysis which would end the outcome assessment window prior to exposure to other UC biologics occurring after the start of the follow-up period will be performed to address this limitation (observational analogue of the PP approach).

On the other hand, the observational analogue of the PP approach in this study may introduce selection bias because it allows for the examination of variables after the start of follow-up to exclude pregnancy episodes. The pregnancy episodes that are excluded may be differentially more or less likely to have study outcomes compared to pregnancy episodes that are included, especially in the case that the measured variables do not include all risk factors that predict adherence.

Similarly, exposures to teratogens occurring after the start of the follow-up period will not be used as an exclusion criteria for any of the study cohorts. This approach poses challenges in estimating the effect of mirikizumab or any of the comparator drugs on a study outcome in the situations where a pregnancy is exposed to a teratogen after the start of follow-up. A sensitivity analysis which would end the outcome assessment window prior to exposure to teratogens occurring after the start of the follow-up period will address this limitation.

In addition because patients will be allowed to enter the study at any time during the pregnancy (depending on the relevant exposure and outcome assessment window), rather than at only fixed time points such as day of last menstrual period or end of first trimester immortal time bias can arise if there are significant differences in the distribution of time to first exposure during the pregnancy between the mirikizumab and comparator exposed cohorts. To account for this potential source of immortal time bias, time between LMP and date of first qualifying exposure will be used as a variable in the propensity score model.

Inclusion/exclusion criteria

For all study cohorts, pregnancies are required to have continuous insurance enrolment (allowing for 30-day gaps) starting 180 days prior to LMP up to the end of pregnancy. The method to create the pregnancy episodes (Moll et al. 2021) has been validated and includes this as a component of building the pregnancy episode to ensure that all pregnancy-related events and exposures can be identified. However, this requirement, excluding pregnancies based on continuous enrolment after the start of the follow-up period, may result in selection bias if the excluded pregnancies have significantly lower or higher risk of experiencing the study outcomes relative to pregnancies that are included, and if this bias is more likely to differentially affect the exposure versus comparator groups. However, for the purposes of this study, it is important to maintain the criteria used to develop the validated algorithm and to accurately determine exposure to medications, to ensure women have not received medications covered by another insurance provider and potentially introducing a bias related to misclassification of exposure status.

Start of the follow-up period

To align with the target trial emulation approach, follow-up will start on LMP if the qualifying medication exposure occurs on or during the 5 half-lives before LMP. If the exposure occurs after LMP, follow-up will start on the first qualifying exposure date after LMP. The baseline period will be 180 days prior to LMP up to the date of first qualifying exposure, meaning there will be a variable amount of time between LMP and start of follow-up. Measuring variables during this time allows for the capture of information from the pregnancy episode that may have been used to make treatment decisions in the real world, and which may also be related to study outcomes. Consequently, patients may have varying amounts of time during which their baseline characteristics are assessed. To address this, the time between LMP and first qualifying exposure will be included in the PS model.

Exposure

Because mirikizumab will have been recently introduced to the market around the time the study begins, the number of exposed pregnancies will likely be limited especially during the early years of the study. Sufficient uptake of mirikizumab use during pregnancy is required before comparative analyses can be initiated.

For the analysis of Objectives 2 and 3, this study prioritises selection of pregnancy episodes with mirikizumab exposure into the mirikizumab UC group, even if they are also exposed to and qualified for inclusion in the comparator treatment group. Prioritizing exposure status may introduce selection bias if use of mirikizumab is associated with underlying factors that influence the risk of the infant and pregnancy study outcomes.

Exposure to mirikizumab and comparator medications relies on pharmacy and or medical claims. Presence of a claim for a filled prescription does not necessarily indicate that the medication was used as prescribed. Mothers who are trying to become pregnant may alter their medication use behaviours and non-compliance with the prescription may result in misclassification in exposure. Medications provided as samples by the healthcare provider will not be observed in administrative claims data.

Additionally, the method used to determine exposure to mirikizumab administered IV by a healthcare provider may result in some misclassification because the mirikizumab-specific HCPCS code will not be available for use when the study begins. This means that a non-specific HCPCS code on medical claims will need to be utilised to identify the induction doses in conjunction with NDC codes on pharmacy claims for the maintenance doses. This may result in assigning incorrect dates for mirikizumab exposure due to the use of the non-specific HCPCS code for other non-mirikizumab treatments coded under the non-specific HCPCS code.

Mirikizumab is indicated for moderate-to-severe UC where the UC was not adequately controlled by other treatments. Therefore, there may be systematic differences in pregnancies receiving mirikizumab treatment compared to those receiving comparator treatments, and this may result in residual confounding. However, the inclusion of variables that may serve as proxies for UC severity (e.g., prior UC hospitalizations, number of unique prior UC medications) in the PS models can mitigate potential imbalances in risk factors that are associated with adverse pregnancy and infant outcomes between the mirikizumab-exposed cohort and comparator treatment-exposed cohort.

Confounders

Administrative claims data used in the study were originally created for reimbursement purposes and not necessarily for research purposes. This may result in some misclassification for variables that are not routinely coded on claims data (e.g., smoking status, alcohol use, and drug abuse/dependence) or absence of key factors (e.g., BMI, genetic factor, breastfeeding), which may confound the observed associations. Furthermore, information from events prior to capture in the database or events that would not be captured in the database are not available. As such, if there is no code corresponding to a variable of interest this variable will be considered as not present.

The measurement of baseline patient characteristics, such as comorbid conditions, is based on data available during the covariate assessment periods. This will likely underestimate the presence of comorbid conditions that do not require frequent interaction with the healthcare system or do not commonly result in a healthcare encounter leading to insurance reimbursement.

Variables assessed after the start of follow-up and variables assessed during the entire pregnancy are not included in the primary analysis outcome models. However, pregnant patients typically seek healthcare during pregnancy (e.g., prenatal care) and variables measured during the pregnancy and after the initiation of follow-up may influence outcomes. While these variables will be reported descriptively, if the distribution of these variables is imbalanced between mirikizumab and comparator groups, there may be uncontrolled confounding in the outcome models.

Outcomes

The study relies on diagnostic and procedure code-based algorithms to identify pregnancy and infant outcomes as well as gestational age at various points in time during the pregnancy. Validated algorithms are used to identify all study outcomes to minimise potential for misclassification of pregnancy and infant outcomes (Palmsten et al. 2014; He et al. 2020; Moll et al. 2021; EC 2022; H4P 2023).

It is possible there may be misclassification of some outcomes due to assumptions made in the construction of the algorithms. For example, the algorithm by Moll et al. (2021) defines pregnancy episodes and gestational age based on a hierarchy of pregnancy episode outcomes and this hierarchy requires that if a woman had an ectopic pregnancy followed shortly by another medical claim where SA is coded, the pregnancy is classified as an ectopic pregnancy. In this scenario, the SA outcome event would not be recorded for this pregnancy, as the pregnancy ended before the SA code occurred.

Many early pregnancy losses do not require the immediate attention of a healthcare provider, do not require a surgical or medical procedure or hospitalization, or have a slowly evolving clinical course. Thus, SAs that do not require medical attention will be missed in this study. However, prior studies have shown that the frequency of live births, SA and SB identified in administrative claims data to be similar to distributions reported across pregnancies in the US (Ailes et al. 2016).

The algorithm for identifying MCM outcomes in administrative insurance claims data was validated using ICD-9-CM diagnosis coding schemes and a validation effort of the algorithm utilizing ICD10-CM has not been undertaken (He et al. 2020; Palmsten et al. 2014). However, a

well-established translation of ICD-9-CM to ICD-10-CM diagnosis codes for MCMs will be applied in this study (CMS 2018; EC 2022). If a validated ICD-10-based MCM algorithm is published during the study period, the current study would evaluate its use and incorporate it into the analysis.

The infant outcomes of MCM and SGA birth will be measured among pregnancies resulting in live births because a live born infant is needed to be able to perform the mother-infant linkage. Pregnancies not ending in a live birth will not be able to assess MCM or SGA birth outcomes. An additional sensitivity analysis is planned to examine MCM and SGA births that are coded on the mothers' claims in an attempt to capture information about these outcomes where there is not a linked infant. However, this will largely underestimate these outcomes occurring among pregnancies not resulting in a live birth because best practice for coding of MCM and SGA birth is to record these on the infant claims and does not include routinely coding of these infant outcomes on maternal claims.

Several outcomes that may be of interest to assess, such as minor congenital malformations, serious infections and elective abortions, will not be evaluated in this study due to the considerable limitations in defining these outcomes in administrative claims data (i.e., lack of validated algorithms to define minor congenital malformations and significant underreporting of elective abortions in administrative claims data). The frequency of serious infections listed in Table 9.8 will be reported descriptively prior to LMP. Serious infections occurring during the pregnancy episode will be reported descriptively.

Sample size

There are many factors which will influence ability to conduct comparative analysis, including factors such as modest target population size, unknown market uptake among women with UC, mother-infant linkage rates, potential sample size attrition in analysis due to use of PS, and relatively rare pregnancy and infant outcomes. The systematic fit-for-purpose assessment of data sources that was undertaken is aimed at selecting a data source that will minimise these factors.

9.10. Other Aspects

None.

10. Protection of Human Subjects

Observational studies will be submitted to ERBs for approval whenever required by local law. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

This study will be conducted in accordance with applicable laws and regulations of the region, country, or countries where the study is being conducted, as appropriate.

11. Management and Reporting of Adverse Events/Adverse Reactions

11.1. Secondary Data Use Study

This is a noninterventional study based on secondary data use, and therefore, no Individual Case Safety Report is required. The study protocol-defined AEs include MCM, SA, SB, SGA, and PTB (see Section 9.3.2). All protocol-defined AE collected will be summarised in the interim and final study report. No other AEs will be collected.

11.2. Product Complaints

Lilly collects product complaints on marketed Lilly products such as drugs, drug/device combinations, medical devices, software as medical device (e.g., mobile medical applications), and comparator product(s) used in postmarketing medical research studies in order to ensure the safety of study participants, monitor quality, and to facilitate process and product improvements.

For Lilly products under evaluation and/or Lilly products not under evaluation but discovered in the course of the study, study personnel are instructed to report product complaints as they would for products in the marketplace.

For non-Lilly products, such as comparator drugs or medical devices, or concomitant drugs or medical devices, study personnel are instructed to report product complaints as they would for products in the marketplace.

12. Plans for Disseminating and Communicating Study Results

Final reports will be submitted to regulatory agencies (EMA and FDA). The study, including the final report, will also be registered in the HMA-EMA Catalogue of RWD studies. The study findings may be submitted to a scientific congress and/or to a peer-reviewed journal.

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Annex 1. Half-lives and Exposure Assessment Windows

Table ANN.1.1. Half-lives Assessment Windows

Drug Group	Drug (Generic Name)	Half-Life (days)	5 × half-life (days)
mirikizumab	mirikizumab	9.3	47
aTNF	infliximab	10	50
	adalimumab	20	100
	golimumab	14	70
Integrin receptor antagonists/mAb	vedolizumab	25	125
interleukin inhibitor/mAb	ustekinumab	19	95
Non-biologics			
- 5-ASA	Sulfasalazine	1	5
	Mesalamine	1	5
	Bals	1	5
	Olsalazine	1	5
- Immunomodulators	MTX	1	5
	Leflunomide	19	95
	Cyclosporine	2	10
	Mercaptopurine	1	5
	Azathioprine	1	5
	Tacrolimus	3	15
	Ozanimod	11	55
	Etrasimod	2	10
JAKi	Upadacitinib	1	5
	Tofacitinib	1	5

Abbreviations: 5-ASA = 5-aminosalicyclic-acid; aTNF = anti-tumour necrosis factor; LMP = last menstrtual period; mAB = monoclonal antibodies; MCM = major congenital malformations; MTX = methotrexate.

Note: All half-lives identified via each drug's label. Half-lives reported in hours have been rounded up to days. Half-lives with 0.5 days indicated have been rounded up to whole numbers.

Annex 2. ENCePP Checklist for Study Protocols

Study title: Observational Study of Pregnancy and Infant Outcomes Among Women Exposed to Mirikizumab During Pregnancy in US-based Administrative Claims Data

EU PAS Register® number: EUPAS105674

Study reference number (if applicable): I6T-MC-B003

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	⊗	☐	☐	6
1.1.2 End of data collection[2]	⊗	☐	☐	9.2.2
1.1.3 Progress report(s)	⊗	☐	☐	4
1.1.4 Interim report(s)	⊗	☐	☐	4
1.1.5 Registration in the EU PAS Register®	⊗	☐	☐	PASSinfo 6
1.1.6 Final report of study results.	⊗	☐	☐	

Study title: Observational Study of Pregnancy and Infant Outcomes Among Women Exposed to Mirikizumab During Pregnancy in US-based Administrative Claims Data

EU PAS Register® number: EUPAS105674

Study reference number (if applicable): I6T-MC-B003

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	⊗	□	□	6
1.1.2 End of data collection[2]	⊗	□	□	9.2.2
1.1.3 Progress report(s)	⊗	□	□	4
1.1.4 Interim report(s)	⊗	□	□	4
1.1.5 Registration in the EU PAS Register®	⊗	□	□	PASSinfo
1.1.6 Final report of study results.	⊗	□	□	6

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	⊗	□	□	7
2.1.2 The objective(s) of the study?	⊗	□	□	8
2.1.3 The target population? (i.e., population or subgroup to whom the study results are intended to be generalised)	⊗	□	□	9.1/9.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	⊗	□	□	8
2.1.5 If applicable, that there is no *a priori* hypothesis?	□	□	□	N/A

Comments:

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g., cohort, case-control, cross-sectional, other design)	⊗	□	□	9.1.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	⊗	□	□	9.1.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	⊗	□	□	9.7.2
3.4 Does the protocol specify measure(s) of association? (e.g., risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	⊗	□	□	9.7.3.2
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g., adverse events that will not be collected in case of primary data collection)	⊗	□	□	11

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	⊗	□	□	9.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	⊗	□	□	9.2.2
4.2.2 Age and sex	⊗	□	□	9.2.1
4.2.3 Country of origin	⊗	□	□	9.4
4.2.4 Disease/indication	⊗	□	□	9.2.1
4.2.5 Duration of follow-up	⊗	□	□	9.2.2
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g., event or inclusion/exclusion criteria)	⊗	□	□	9.2.1

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	⊗	□	□	9.3.1
5.2 Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	⊗	□	□	9.3.1
5.3 Is exposure categorised according to time windows?	⊗	□	□	9.2.1.3
5.4 Is intensity of exposure addressed? (e.g., dose, duration)	⊗	□	□	9.3.1
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	⊗	□	□	9.3.1
5.6 Is (are) (an) appropriate comparator(s) identified?	⊗	□	□	9.2/Table 9.5

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	⊗	☐	☐	9.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	⊗	☐	☐	9.3.2
6.3 Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	⊗	☐	☐	9.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	⊗	☐	N/A

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	⊗	□	□	9.7.3
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	⊗	□	□	9.7.2
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	⊗	□	□	9.7.3.3

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g., collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	⊗	□	□	9.2.1.3

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	⊗	□	□	9.3.1
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	⊗	□	□	9.1.2.1
9.1.3 Covariates and other characteristics?	⊗	□	□	9.3.3
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	⊗	□	□	9.3.1
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	⊗	□	□	9.3.2
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	⊗	□	□	9.3.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	⊗	□	□	9.3.1
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	⊗	□	□	9.3.2
9.3.3 Covariates and other characteristics?	⊗	□	□	9.3.3

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	⊗	□	□	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	⊗	□	□	9.7
10.2 Is study size and/or statistical precision estimated?	⊗	□	□	9.5
10.3 Are descriptive analyses included?	⊗	□	□	9.7.1/9.7.2
10.4 Are stratified analyses included?	⊗	□	□	9.7.3
10.5 Does the plan describe methods for analytical control of confounding?	⊗	□	□	9.7.3.1
10.6 Does the plan describe methods for analytical control of outcome misclassification?	⊗	□	□	9.7.3.3
10.7 Does the plan describe methods for handling missing data?	⊗	□	□	9.4/9.7.1
10.8 Are relevant sensitivity analyses described?	⊗	□	□	9.7.3.3

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	⊗	□	□	9.6
11.2 Are methods of quality assurance described?	⊗	□	□	9.6/9.8
11.3 Is there a system in place for independent review of study results?	⊗	□	□	9.8

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	⊗	□	□	9.9
12.1.2 Information bias?	⊗	□	□	9.9
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	⊗	□	□	9.9
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	⊗	□	□	9.5.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/Institutional Review Board been described?	⊗	□	□	10
13.2 Has any outcome of an ethical review procedure been addressed?	⊗	□	□	10
13.3 Have data protection requirements been described?	⊗	□	□	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	⊗	□	□	5

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g., to regulatory authorities)?	⊗	□	□	12
15.2 Are plans described for disseminating study results externally, including publication?	⊗	□	□	12

Comments:

Name of the main author of the protocol: PPD

Date: 04/03/2024

Signature: PPD

Annex 3. Appendices

Appendix A Clinical Codes for Identifying Pregnancy

Appendix B Minimum Allowable Days Between Pregnancies

Appendix C Prenatal Windows and Minimum Spacing

Appendix D Teratogen-Specific Half-life

Codelists to be provided in the SAP:

Appendix E Detailed Covariate Code List

Appendix F Inclusion/Exclusion Criteria Definitions

Appendix G Teratogenic Medication Code List

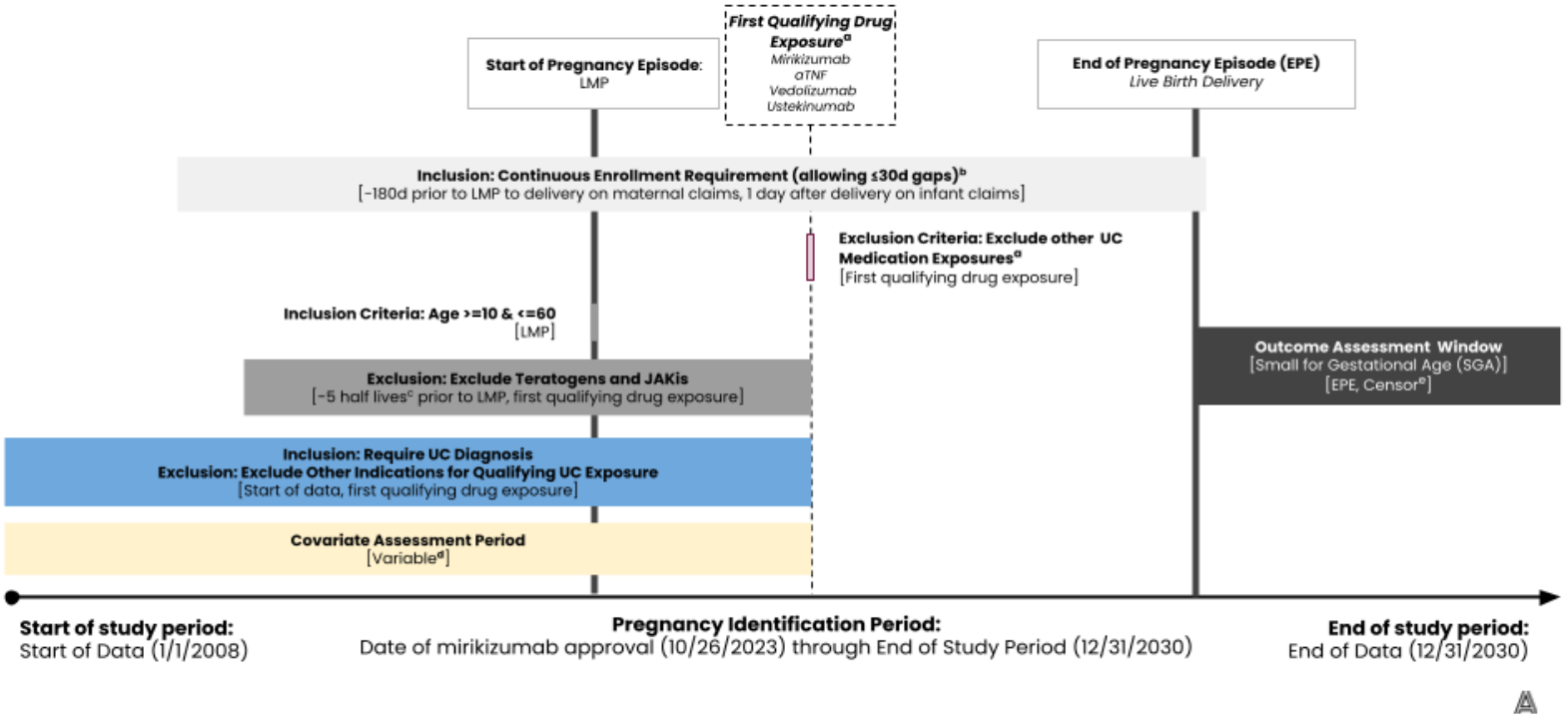
Appendix H Mirikizumab and Comparator Code Lists

Appendix I Primary Objective MCM Outcome Diagnostic Code List

Appendix J Primary Objective MCM Outcome Procedure Code List

Appendix K Secondary Objective Outcomes Code List

Annex 4. Study Figures for Other Outcomes



Abbreviations: aTNF = anti-tumour necrosis factor; d = day(s); JAKi = Janus kinase inhibitor; LMP = last menstrual period; SGA = small for gestational age; UC = ulcerative colitis.

a The first qualifying drug exposure during the exposure assessment window is the exposure that determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with >1 UC exposure on the first qualifying exposure date will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF are started on the same day would not qualify and would, therefore, be excluded from this study.

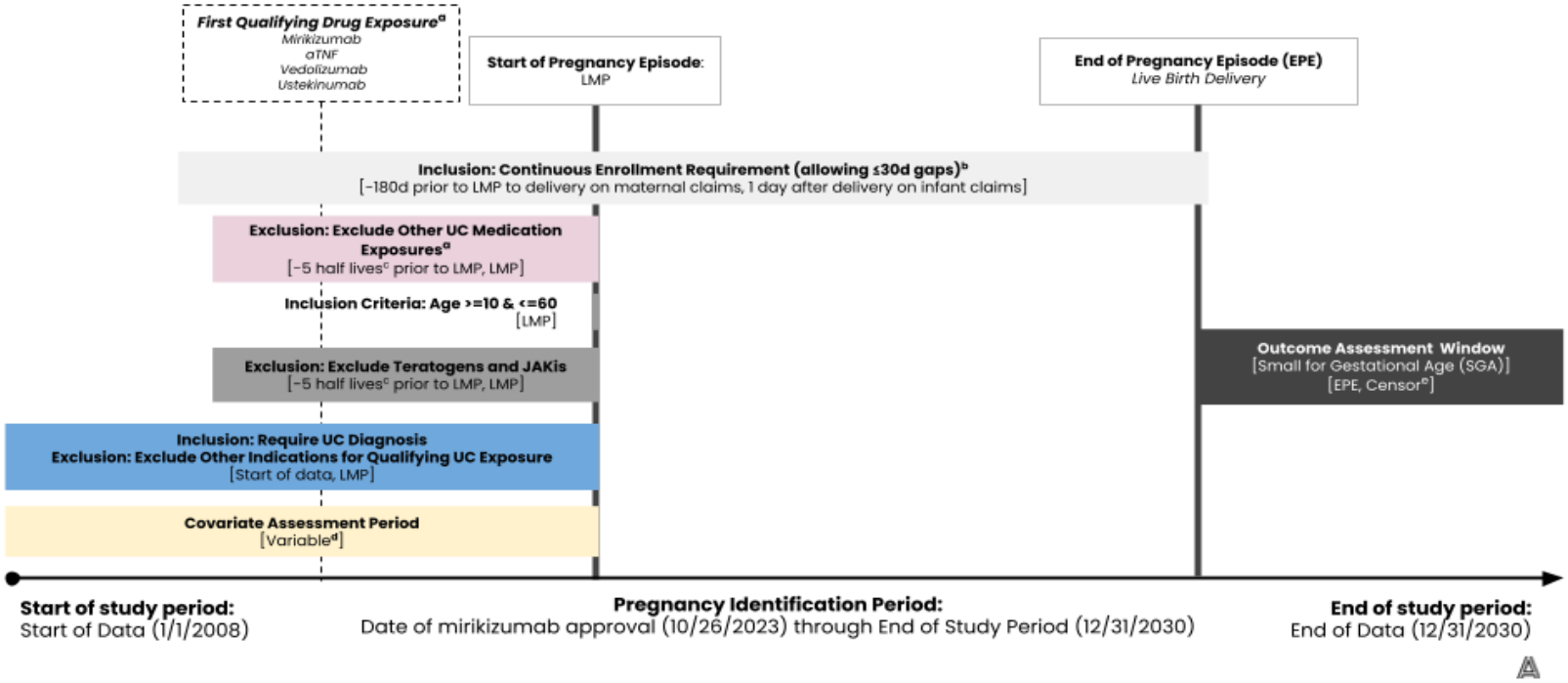
b The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

c The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

d Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

e All pregnancy episodes must end in a live birth to be assessed for this outcome. Mother-infant linkage is also required, and LMP must occur 30 days + the duration of a full-term pregnancy prior to the end of data for this outcome. SGA is assessed on infant claims from birth until the occurrence of either a diagnosis of SGA, 30 days, infant disenrollment (≤30 day gaps allowed), infant death, or end of the study period, whichever occurs first.

Figure ANN.4.1. Study design for assessment of small for gestational age (Objectives 2 and 3) where the first qualifying exposure is during pregnancy episode.



Abbreviations: aTNF = anti-tumour necrosis factor; d = day(s); JAKi = Janus kinase inhibitor; LMP = last menstrual period; SGA = small for gestational age; UC = ulcerative colitis.

a The first qualifying drug exposure in the exposure assessment window (determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Section 9.2 and 9.3.1. Pregnancies with >1 UC medication exposure in the 5 half-lives prior to LMP will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF occur in the 5 half-lives prior to LMP cannot qualify for any cohort and would, therefore, be excluded from this study.

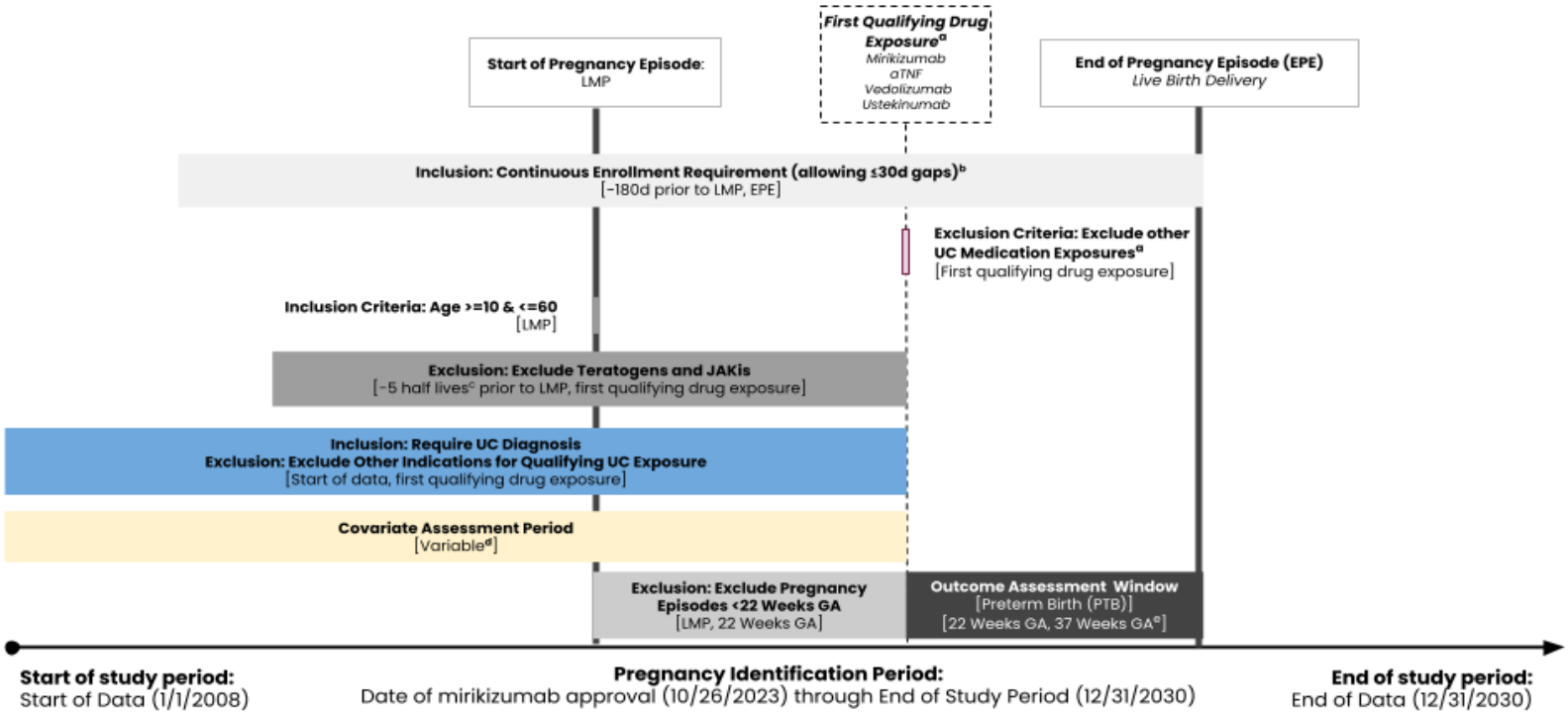
b The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

c The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

d Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

e All pregnancy episodes must end in a Live Birth to be assessed for this outcome. Mother-infant linkage is also required, and LMP must occur 30 days + the duration of a full-term pregnancy prior to the end of the study period. SGA is assessed on infant claims from birth until the occurrence of a diagnosis of SGA, 30 days infant disenrollment (≤30 day gaps allowed), infant death, or end of the study period, whichever occurs first.

Figure ANN.4.2. Study design for assessment of small for gestational age (Objectives 2 and 3) where the first qualifying exposure occurs in 5 half-lives prior to LMP.



Abbreviations: aTNF = anti-tumour necrosis factor; d = day(s); GA = gestational age; JAKi = Janus kinase inhibitor; LMP = last menstrual period; PTB = pre-term birth; UC = ulcerative colitis.

a The first qualifying drug exposure during the exposure assessment window is the exposure that determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with >1 UC exposure on the first qualifying exposure date will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF are started on the same day would not qualify and would, therefore, be excluded from this study.

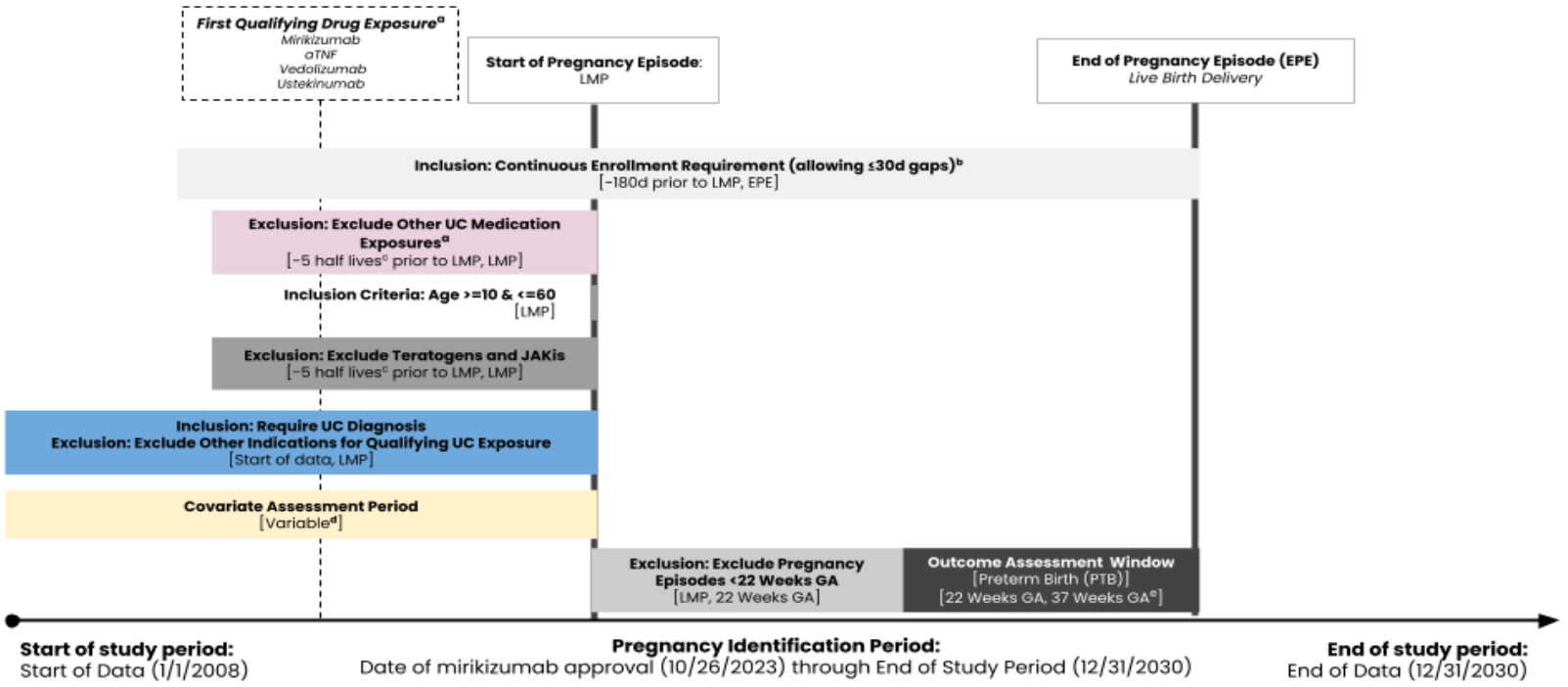
b The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

c The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

d Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

e Follow-up assessed on mothers' claims data. By definition of PTB, the outcome cannot occur until 22 weeks' gestation. Thus, PTB is assessed from 22 (inclusive) to <37 weeks' gestation. Only pregnancies ending in live birth are considered eligible for this outcome.

Figure ANN.4.3. Study design for assessment of preterm birth (Objectives 2 and 3) where the first qualifying exposure is during pregnancy episode.



Abbreviations: aTNF = anti-tumour necrosis factor; d = day(s); GA = gestational age; JAKi = Janus kinase inhibitor; LMP = last menstrual period; PTB = pre-term birth; UC = ulcerative colitis.

a The first qualifying drug exposure in the exposure assessment window determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with more than one UC medication exposure in the 5 half-lives prior to LMP will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF occur in the 5 half-lives prior to LMP cannot qualify for any cohort and would therefore be excluded from this study.

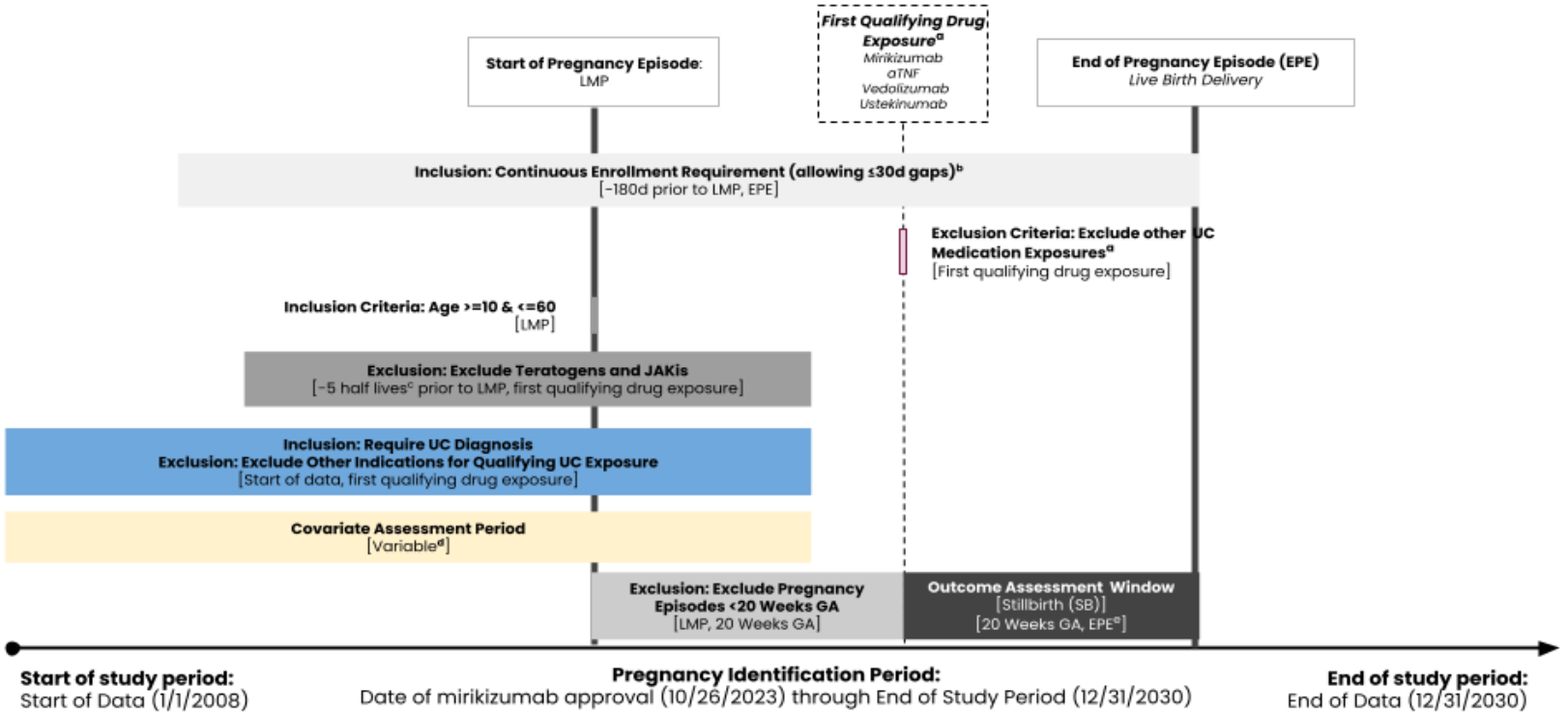
b The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

c The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

d Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

e Follow-up assessed on mothers' claims data. By definition of PTB, the outcome cannot occur until 22 weeks' gestation. Thus, PTB is assessed from 22 (inclusive) to <37 weeks' gestation. Only pregnancies ending in live birth are considered eligible for this outcome.

Figure ANN.4.4. Study design for assessment of preterm birth (Objectives 2 and 3) where the first qualifying exposure occurs in 5 half-lives prior to LMP.



Abbreviations: aTNF = anti-tumour necrosis factor; d = day(s); GA = gestational age; LMP = last menstrual period; SB = stillbirth; UC = ulcerative colitis.

a The first qualifying drug exposure during the exposure assessment window is the exposure that determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with more than one UC exposure on the first qualifying exposure date will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF are started on the same day would not qualify and would, therefore, be excluded from this study.

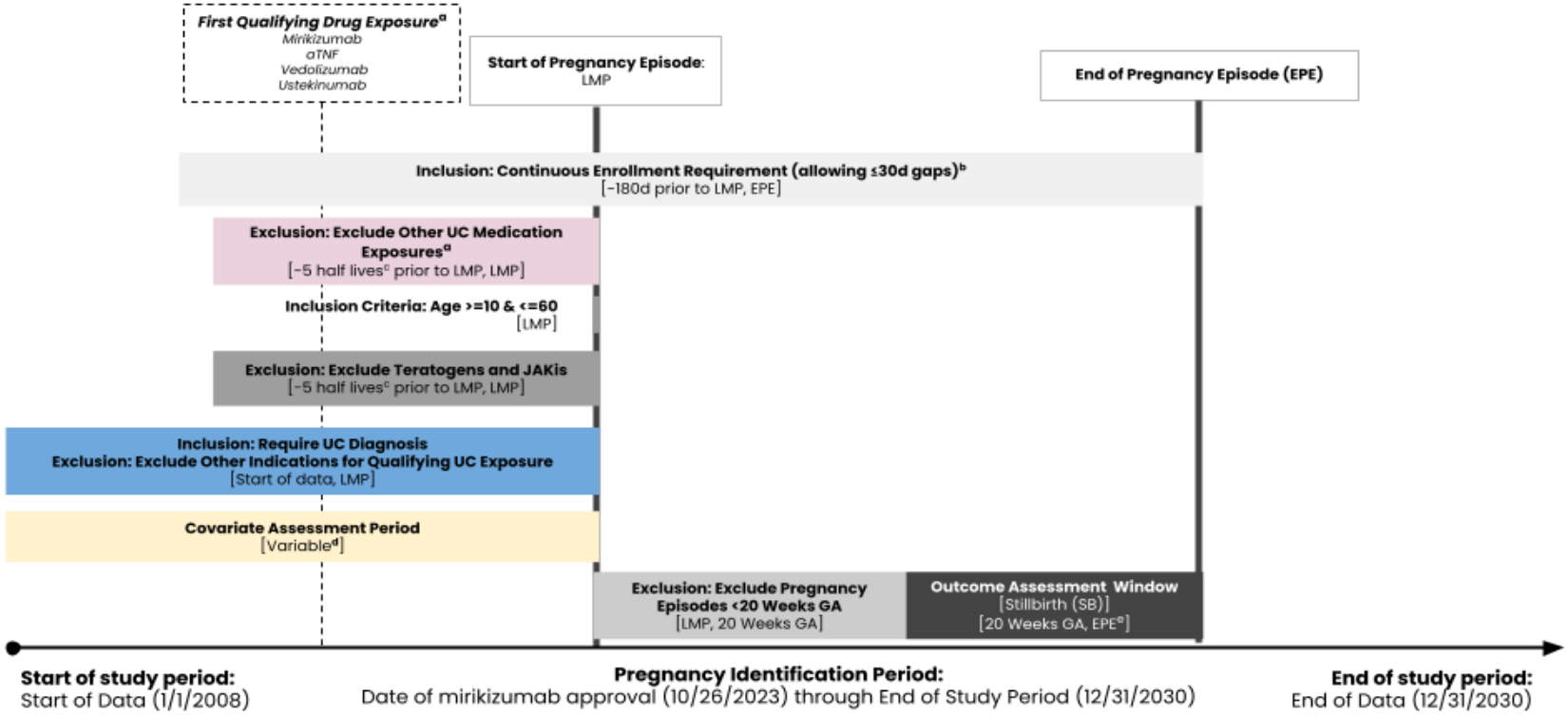
b The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

c The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

d Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

e Follow-up assessed on mothers' claims data. By definition of SB, the outcome cannot occur until 20 weeks' gestation. Thus, SB is assessed starting at 20 weeks' gestation. Only pregnancies ≥ 20 weeks' gestation will be eligible for the assessment of this outcome.

Figure ANN.4.5. Study design for assessment of stillbirth (Objectives 2 and 3) where the first qualifying exposure is during pregnancy episode.



Abbreviations: aTNF = anti-tumour necrosis factor; d = day(s); GA = gestational age; LMP = last menstrual period; SB = stillbirth; UC = ulcerative colitis.

a The first qualifying drug exposure in the exposure assessment window determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with more than one UC medication exposure in the 5-half-lives prior to LMP will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF occur in the 5 half-lives prior to LMP cannot qualify for any cohort and would therefore be excluded from this study.

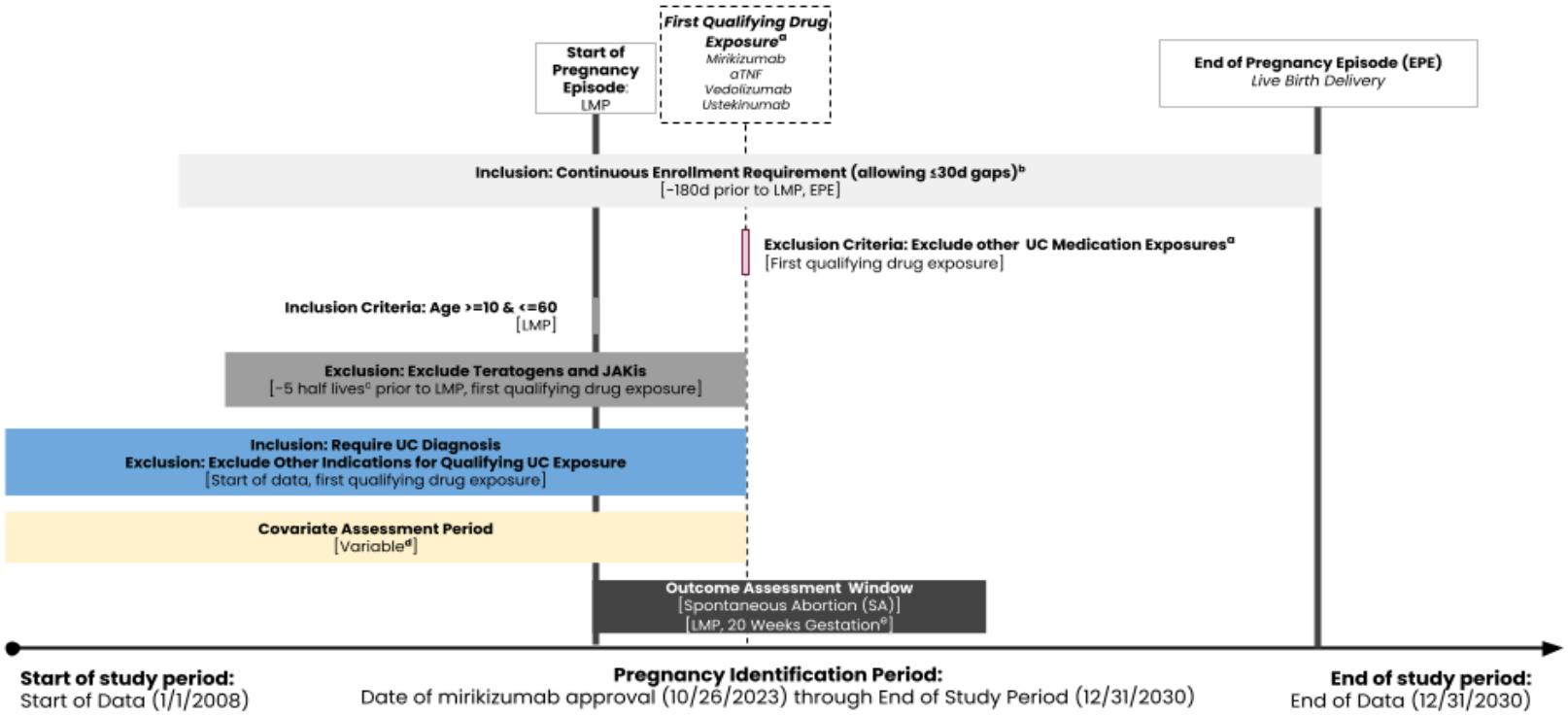
b The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

c The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

d Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

e Follow-up assessed on mothers' claims data. By definition of SB, the outcome cannot occur until 20 weeks' gestation. Thus, SB is assessed starting at 20 weeks' gestation. Only pregnancies ≥ 20 weeks' gestation will be eligible for the assessment of this outcome.

Figure ANN.4.6. Study design for assessment of stillbirth (Objectives 2 and 3) where the first qualifying exposure occurs in 5 half-lives prior to LMP.



Abbreviations: aTNF = anti-tumour necrosis factor; JAKi = Janus kinase inhibitor; LMP = last menstrual period; SA = spontaneous abortion; UC = ulcerative colitis.

a The first qualifying drug exposure during the exposure assessment window is the exposure that determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with more than one UC exposure on the first qualifying exposure date will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF are started on the same day would not qualify and would therefore be excluded from this study.

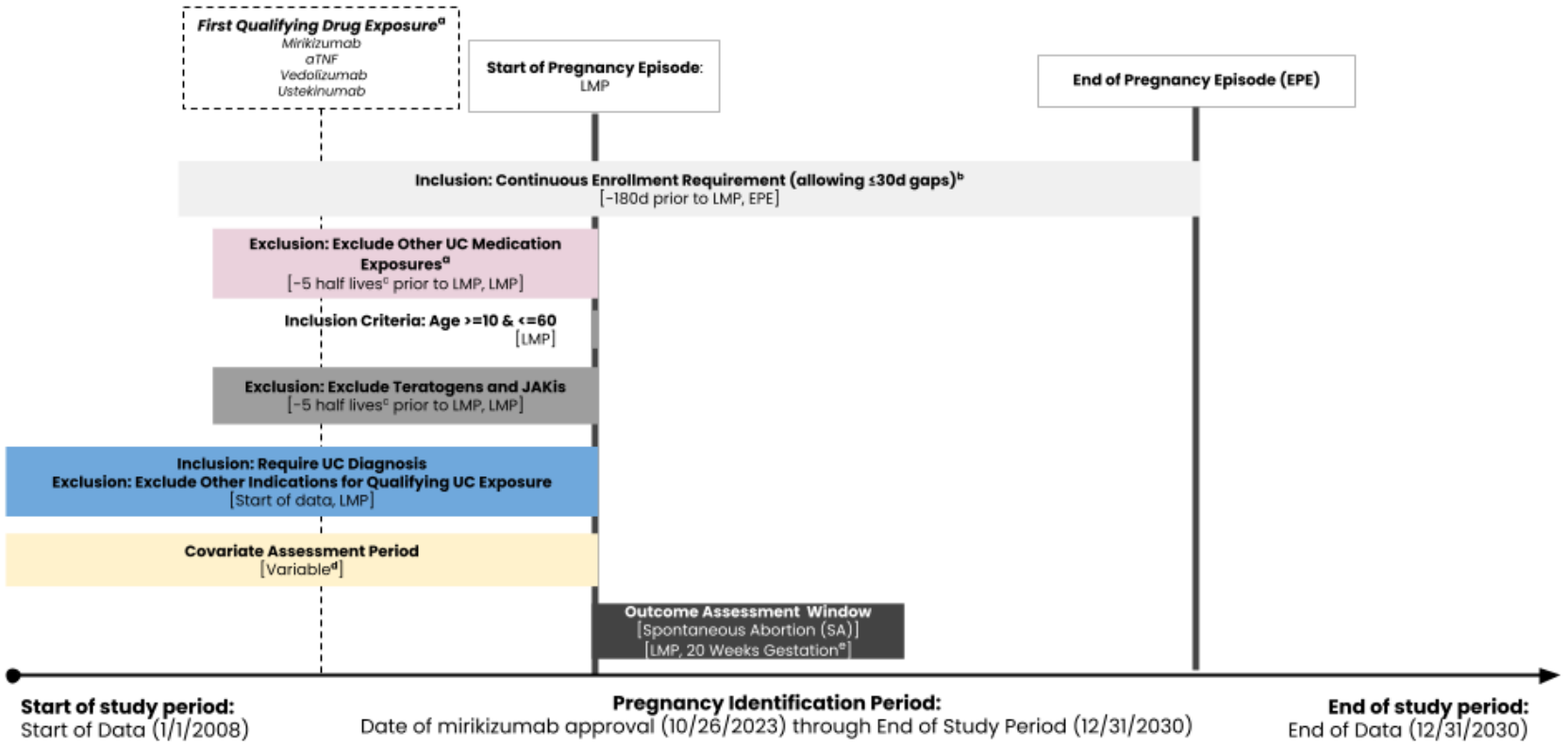
b The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

c The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

d Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

e Follow-up assessed on mothers' claims data. SA is assessed prior to 20 weeks' gestation. By definition of SA, the outcome cannot occur at 20 weeks' gestation or later. Thus, SA is assessed until 20 weeks' gestation. Only pregnancies < 20 weeks' gestation will be eligible for the assessment of this outcome.

Figure ANN.4.7. Study design for assessment of spontaneous abortion (Objectives 2 and 3) where the first qualifying exposure is during pregnancy episode.



Abbreviations: aTNF = anti-tumour necrosis factor; JAKi = Janus kinase inhibitor; LMP = last menstrual period; SA = spontaneous abortion; UC = ulcerative colitis.

a The first qualifying drug exposure in the exposure assessment window determines the cohort classification. UC medication exposures include mirikizumab, aTNFs, vedolizumab, or ustekinumab. Exposures must occur in the relevant exposure assessment window as outlined in Sections 9.2 and 9.3.1. Pregnancies with more than one UC medication exposure in the 5-half-lives prior to LMP will be excluded from all cohorts. For example, a pregnancy where both mirikizumab and aTNF occur in the 5 half-lives prior to LMP cannot qualify for any cohort and would therefore be excluded from this study.

b The Moll algorithm used to identify pregnancy episodes requires health plan enrolment throughout the pregnancy episode. Therefore, all pregnancy episodes will have continuous enrolment during the entire baseline period through the end of the pregnancy.

c The exposure assessment window and exclusion window is dependent on the half-life of each drug exposure (Annex 1).

d Covariate assessment windows vary by covariate and outcome. For specific time periods of assessment, see Table 9.6.

e Follow-up assessed on mothers' claims data. SA is assessed prior to 20 weeks' gestation. By definition of SA, the outcome cannot occur at 20 weeks' gestation or later. Thus, SA is assessed until 20 weeks' gestation. Only pregnancies < 20 weeks' gestation will be eligible for the assessment of this outcome.

Figure ANN.4.8. Study design for assessment of spontaneous abortion (Objectives 2 and 3) where the first qualifying exposure occurs in 5 half-lives prior to LMP.