PASS/FDA PMR Information

Title	Pregnancy Exposures and Outcomes in Women with Inflammatory Bowel Disease Treated with Risankizumab: A Cohort Study Utilizing Large Electronic Healthcare Databases with Mother-Baby Linkage in the United States
Protocol version identifier	Version 2.0
Date of last version of protocol	24 September 2024
EU PAS register number	EUPAS1000000283
Active substance	Risankizumab (ATC code L04AC18)
Medicinal product	Risankizumab: Skyrizi®
Product reference	EMEA/H/C/004759, Post-Authorisation Measure 009 US: BLA 761105 and BLA 761262, PMR 4294-3
Procedure number	Not applicable
Marketing authorisation holder(s)	EU: AbbVie Deutschland GmbH & Co. KG US: AbbVie Inc
Joint PASS	No
Research question and objectives	The study aim is to evaluate the safety of risankizumab during pregnancy in women with moderate-to-severe inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC). The risk of pre-specified pregnancy, birth and infant outcomes will be estimated in pregnant women exposed to risankizumab, and in a comparator population including pregnant women with moderate-to-severe IBD exposed to comparator biologics, including anti-tumor necrosis factor (TNF), integrin receptor antagonist biologics or their biosimilars (comparator biologic-exposed group). The primary outcome of this cohort study is major congenital malformations of the infant. Secondary outcomes include select pregnancy outcomes (live birth, spontaneous abortion, elective abortion, stillbirth) and infant outcomes (premature birth, small for gestational age (SGA), neonatal deaths, serious infections).
Country(-ies) of study	United States

Abstract

Rationale and Background

Risankizumab is an interleukin (IL)-23 antagonist approved for the treatment of moderate-to-severe plaque psoriasis, psoriatic arthritis, and inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC), in Europe and the United States (US). Limited information can be obtained from risankizumab clinical trials on the safety of risankizumab exposure during pregnancy. Therefore, information about the association between risankizumab exposure during pregnancy and maternal, fetal and infant outcomes is limited.

Research Question and Objectives

The study aim is to evaluate the safety of risankizumab during pregnancy in women with moderate-to-severe IBD, which includes CD and UC. The risk of pre-specified pregnancy, birth and infant outcomes will be estimated in pregnant women with moderate-to-severe IBD exposed to risankizumab and in a comparator population of pregnancies in women with moderate-to-severe IBD exposed to comparator biologics (anti-tumor necrosis factor (TNF), integrin receptor antagonist biologics or their biosimilars [comparator biologic-exposed group]).

The primary outcome of this cohort study is major congenital malformations (MCMs) of the infant among live birth pregnancies.

Secondary outcomes include the following:

- Pregnancy outcomes: live birth, spontaneous abortion, elective abortion, stillbirth
- Infant outcomes: premature birth, small for gestational age (SGA), neonatal deaths, serious infections

Secondary descriptive analyses will estimate rates of MCMs and other pregnancy and infant outcomes among an IBD group treated with non-biologic medications (non-biologic treated group) to serve as a frame of reference for descriptive purposes.

Study Design

The study will be a population-based, non-interventional, cohort study of pregnant women with moderate-to-severe IBD, which includes CD and UC. The primary comparison will be among women with moderate-to-severe IBD exposed to risankizumab versus those exposed to the

comparator treatment group during pregnancy. A secondary descriptive analysis will be conducted among a non-biologic treated group (pregnant women diagnosed with IBD and treated with a non-biologic medication used for IBD treatment, and not exposed to risankizumab or other biologics). The primary outcome of interest will be MCMs. Additional outcomes of interest include other adverse infant outcomes (premature birth, SGA, neonatal deaths, serious infections) and pregnancy outcomes (live birth, spontaneous abortion, elective abortion, stillbirth). The study will be conducted using US administrative claims databases that have longitudinal capture of medical encounters and prescription medication exposures for large cohorts. Medical charts will be reviewed by board certified teratologists to confirm MCMs, the primary outcome of interest.

Population

This study will be conducted in several secondary data sources in the US that participate in the [redacted].

The study population will include pregnant women (ages 15 to 55 years at the start of pregnancy) diagnosed with IBD and exposed to a medication (biologic or non-biologic) used in the treatment of IBD. Pregnancies with estimated start dates occurring during the period 01 June 2022 to Q2 2029, and infants born to the women, will be included. Additional eligibility criteria will include continuous health plan enrollment with medical and pharmacy benefits for at least 272 days prior to estimated start of pregnancy until the pregnancy end date, allowing gaps of up to 45 days in coverage. The 272-day pre-pregnancy period will allow identification of potential confounders of interest in the electronic healthcare databases.

Women will be selected based on the use of risankizumab or comparator biologics during pregnancy, excluding those exposed to both treatments during the same pregnancy. A third group including patients treated with non-biologic medications used for the treatment of IBD will be used for descriptive purposes.

Pregnancies ending in gestational trophoblastic disease or ectopic pregnancy will be excluded from the analysis. Additional exclusion criteria will include exposure to medications that present a known increased risk for fetal malformation, exposure to ustekinumab (an IL-12/IL-23 inhibitor) or mirikizumab (an IL-23 inhibitor), or exposure to a Janus kinase (JAK) inhibitor or

sphingosine 1-phosphate receptor (S1PR) modulator used in the treatment of IBD (IBD medications that have shown evidence of fetal risk in animal studies).

For analyses evaluating infant outcomes (MCMs and other infant outcomes), pregnancies for which the infant is identified with a chromosomal or genetic anomaly will also be excluded.

For eligible pregnancies ending in a live birth, mothers will be linked to their infants using the Food and Drug Administration (FDA) Sentinel Initiative Program mother-infant linkage methodology which utilizes health plan administrative claims data and birth certificate data (as available).

The study will examine pregnancy outcomes in the [redacted] population of pregnant women meeting eligibility criteria. Infant outcomes will be assessed in the subset of live birth pregnancies linked to infant records.

Variables

Information about demographics, maternal age, pregnancy start and trimester (estimated using claims-based algorithms), IBD diagnoses, maternal comorbidities, obstetric history, and lifestyle factors, relevant treatments during and prior to pregnancy, other proxy markers of disease activity/severity, pregnancy outcomes (live birth, spontaneous abortions, stillbirths, elective abortions) and infant outcomes (MCMs, premature birth, SGA, neonatal deaths, serious infections) will be collected from the healthcare electronic databases (health plan enrollment and claims data and integrated healthcare systems data), supplemented with medical records to confirm MCMs. All conditions used to define the population, exposures, comorbidities, and outcomes will be identified using validated algorithms, where available.

Data Sources

This study will be conducted using health plan administrative claims data in the [redacted]. [redacted] provides a framework for private-sector entities (e.g., regulated industry, academic institutes) to leverage the [redacted] and analytic tools. FDA Sentinel is a national electronic system for active surveillance of the safety of drugs, biologics, vaccines, and medical devices in the US, established under the Sentinel Initiative. [redacted] uses a common data model for standardization of demographic and clinical data elements and has routine analytical tools to permit rapid queries, including descriptive analyses and

complex methodologies (e.g., comparative analyses), [redacted]. [redacted] and is expected to be largely representative of the commercially-insured population in the US. [redacted] currently includes approximately 83 million patient-lives. Health plan claims and integrated healthcare systems data included in the [redacted] will be supplemented with medical records to confirm MCMs.

Study Size

The sample size will be influenced by the uptake of risankizumab and comparators (biologic therapies for IBD) among pregnant women in the study population. All pregnant women who are exposed to risankizumab and meet the study inclusion/exclusion criteria will be included in this study.

Assuming a two-sided test, a type 1 error of 0.05 for a two-group Chi-square test of equal proportions, a 4% prevalence of MCMs in the comparator biologic-exposed group, and a [redacted] comparator biologic users, [redacted] (live birth pregnancies linked to infant records) from the risankizumab-exposed group (exposed during the first trimester) and [redacted] comparator biologic-exposed group will allow us to achieve 80% power to detect a risk ratio (RR) of 2.5 for the primary safety outcome, MCMs.

Based on exposure data included in annual monitoring reports, if projected target numbers of pregnancies are not reached [redacted] a stepwise approach for inclusion of additional data sources may be applied to increase sample size. [redacted]. If projected target numbers are not reached after inclusion of additional partners, the termination, modification, or extension of the study will be discussed in collaboration with the US FDA and European Medicines Agency (EMA).

Data Analysis

MCMs (primary outcome of interest) and other infant/birth outcomes (premature birth, small for gestational age (SGA), neonatal deaths, serious infections) will be assessed among eligible live birth pregnancies linked to infant records. Pregnancy outcomes will be assessed in the population

of livebirth, spontaneous abortion, elective abortion, and stillbirth pregnancies meeting eligibility criteria.

Descriptive analyses will be performed to estimate the prevalence of risankizumab and comparator treatment exposures during pregnancy among women with IBD. Exposures will be described overall and by trimester, specific IBD condition (CD, UC), maternal age, and calendar year of pregnancy outcome.

Separate propensity scores will be estimated for analyses conducted among all eligible pregnancies and among the subset of live birth pregnancies linked to infant records. We will match comparators on propensity score and other baseline variables, which may include Network Partner, specific IBD condition, maternal age, and timing of exposure.

The prevalence (%) of the main outcome (MCMs) and additional outcomes, including other adverse infant outcomes and pregnancy outcomes (live birth, spontaneous abortion, elective abortion, stillbirth), and their 95% confidence intervals (CIs) will be calculated among eligible risankizumab-exposed pregnancies and the corresponding matched comparator biologic-exposed pregnancies. For the main outcome, only MCM cases confirmed within the medical records will be included in the numerator of prevalence estimates.

Based on sample size estimation for the minimum number of live birth pregnancies needed to ensure 80% power for comparative analysis of the main outcome (MCMs), a comparative analysis of the risk of infant and pregnancy outcomes of risankizumab-exposed versus comparator biologic pregnancies will be conducted [redacted]

The prevalence of the primary outcome (MCMs) and secondary outcomes will be compared for eligible exposed and matched comparator pregnancies and prevalence ratios with 95% CIs will be reported.

All analyses will be stratified by stage of pregnancy exposure (early stage: pregnancy start through first trimester exposure; mid-to-late stage: second or third trimester exposure). Exposure in early pregnancy (pregnancy start through first trimester; period of organogenesis) will be the primary period for evaluation, given that exposures after this period would not be causally related to MCMs (the primary outcome).

Descriptive analyses will estimate the prevalence of the primary and secondary outcomes stratified by specific IBD condition (CD, UC).

Additional secondary analyses will include estimation of the prevalence of MCMs and other infant outcomes and the incidence of pregnancy outcomes among the non-biologic treated group for descriptive purposes. While biologic-exposed cohorts (risankizumab-exposed and comparator biologic-exposed groups) are comprised of moderate to severe IBD cases, it should be noted that non-biologic medications are used to treat mild IBD, and disease severity can independently influence pregnancy outcomes in IBD patients.

These methodologies and additional secondary and sensitivity analyses will be described in detail in a Statistical Analysis Plan (SAP).

Milestones

AbbVie will initiate the study upon regulatory approval of the study protocol by EMA and FDA. Annual surveillance reports will be generated starting from 2025 to 2032, with the exception of 2028. A study progress report will be completed in 2028. A final study report will be submitted to the EMA and FDA by June 2033.