Janssen EMEA Medical Affairs

Observational Study Protocol

Ustekinumab and risk of small for gestational age in inflammatory bowel disease pregnancies: data from the DUMBO registry

Ustekinumab SGA DUMBO Study

Protocol: PCSIMMA0309

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STUDY INFORMATION

Title:	**Ustekinumab and risk of small for gestational age in inflammatory bowel disease pregnancies: data from the DUMBO registry**
Protocol version:	1.0
Date of last version of the protocol:	Date
EU PAS Register No:	Not registered
Active substance (INN common name):	Ustekinumab
Pharmaco-therapeutic group (ATC Code):	L04AC05
Medicinal product(s):	STELARA®
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Procedure number:	EMA procedure number(s) if applicable: EMA/XX/XX/<XXX>
Name of Marketing Authorization Holder(s)	Janssen-Cilag International NV
Joint PASS	No
Research question and objectives	**Research Question :** In pregnant women with IBD, is exposure to ustekinumab during pregnancy associated with an increased risk of delivering small for gestational age (SGA) infants compared with exposure to anti-TNFα agents (primary comparator), and compared with exposure to immunomodulators or no immunomodulatory/biologic therapy (secondary comparators), after adjusting for disease activity and other confounders? **Objectives :** The objective of the study is to compare the incidence rates of SGA infants in pregnant women with IBD exposed to ustekinumab (including biosimilars) during pregnancy to those exposed to anti-TNFα agents (infliximab, adalimumab, golimumab, including biosimilars), to those exposed to immunomodulators (including corticosteroids) and to those not exposed to either biologics or immunomodulators
Country(-ies) of study	Spain
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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description of Abbreviated Term
AEG	Asociación Española de Gastroenterología
BMI	Body mass index
CD	Crohn's disease
CDAI	Crohn's disease activity index
DUMBO	Safety Of IB(D) Dr(U)gs During Pregnancy And Breastfeeding (M)others And (B)abies' (O)utcomes
FcRn	Neonatal Fc receptor
GETECCU	Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa
IBD	Inflammatory Bowel Diseases
IBD-U	unclassified IBD
ICU	Intensive care unit
IPTW	Inverse probability of treatment weighting
IQR	Interquartile range
JAK	Janus Kinase
MedDRA	Medical Dictionary for Regulatory Activities
REDCap	Research Electronic Data Capture
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event
SD	Standard deviation
SGA	Small for gestational age
TNF	Tumor necrosis factor
UC	Ulcerative colitis
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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4. SYNOPSIS

Protocol Title: Ustekinumab and risk of small for gestational age in inflammatory bowel disease pregnancies: data from the DUMBO registry (1.0, 27 January 2026)

Sponsor's Responsible Party: PPD, MD, PhD (Main Author)
NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

Background and Rationale: Inflammatory bowel disease (IBD) predominantly affects individuals during their reproductive years, with an increasing number of pregnant women being treated with biologic therapies. Among these agents, ustekinumab, an IgG1 monoclonal antibody targeting the p40 subunit of IL-12/23, is increasingly used in patients with either Crohn's disease (CD) or ulcerative colitis (UC). Ustekinumab can cross the placenta via the neonatal Fc receptor (FcRn), leading to in utero fetal exposure, particularly during the second and third trimesters. Despite this potential for fetal drug exposure, there is still a need for broader real-world evidence on pregnancy and neonatal outcomes associated with ustekinumab use. Until recently, no adverse pregnancy outcomes had been identified in association with ustekinumab exposure. However, a recent study raised concerns about a possible increased risk of infants being born small for gestational age (SGA) in women with IBD exposed to ustekinumab during pregnancy when compared to women exposed to anti-tumor necrosis factor α (TNFα). That study has important limitations including but not limited to the retrospective claims-based design, where IBD activity and residual confounding may not be fully captured. This study aims to address these gaps by leveraging prospectively collected clinical data to explore the risk of SGA associated with ustekinumab exposure in a real-world IBD pregnancy cohort.

Research Question and Objectives: The objective of the study is to compare the incidence rates of SGA infants born to women with IBD exposed to ustekinumab (including biosimilars) during pregnancy to those exposed to anti-TNFα agents (infliximab, adalimumab, golimumab, including biosimilars) and to those not exposed to biologics (immunomodulators and/or steroids or no treatment).

Study Design: The study follows an observational design, based on analysis of data from the DUMBO registry, a prospective Spanish cohort of pregnant women with IBD supported by Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU). The registry prospectively collects clinical, treatment, and outcome data. Maternal demographic and clinical data are collected at baseline (visit 0), defined as the time of study enrolment (after confirmation of pregnancy but before the end of the second trimester). The exposure start date for treatments of interest is defined as the date of first administration of each specific treatment or the date of the last menstrual period if the patient was already under the treatment. Patients will be classified according to treatments received at conception and/or at any time during pregnancy.

Setting and Study Population: Data will be drawn from the DUMBO registry, a prospective multicenter observational registry enrolling pregnant women with IBD over a 5-year period at multiple centres across Spain. Treatment is decided independently by the treating physician according to local practice.

Inclusion Criteria

- Pregnant women with confirmed IBD (CD, UC, IBD-U) recruited into the DUMBO registry before week 28 of gestation.
- Exposed to mesalazine, immunomodulators including corticosteroids, anti-TNFα agents, ustekinumab or not exposed to any treatment at any time during pregnancy or within 3 months prior to conception.

Exclusion Criteria

- Patients exposed to known teratogens from conception through the first trimester.
- Patients exposed to targeted small molecules (eg. JAKi, S1P modulators), or biologics other than anti-TNFα agents or ustekinumab.
- Lack of informed consent, or loss to follow-up prior to delivery.

Variables

Baseline Information
Maternal demographic and clinical data (disease characteristics, activity and treatment) will be extracted. These include: type of IBD, age at diagnosis, IBD activity and severity based on the Crohn's Disease Activity Index (CDAI) for CD or the Partial Mayo Score for UC, comorbidities, IBD treatments, substance use before pregnancy, obstetric history, and anthropometric data.

Exposure Groups
Drugs will be identified at the ingredient level and exposure groups are defined as:

- Group 1: Mesalazine or no treatment-exposed cohort
- Group 2: Immunomodulators-exposed cohort (including corticosteroids).
- Group 3: Anti-TNFα-exposed cohort (infliximab, adalimumab, golimumab, including biosimilars, with or without immunomodulators).
- Group 4: Ustekinumab-exposed cohort (including biosimilars, with or without immunomodulators).

Children are assigned based on the treatment their mother received during pregnancy and/or conception.

Primary Outcome
SGA is defined as birth weight below the 10^{th} percentile for gestational age and sex. For term newborns (≥37 weeks) WHO growth standards will be used; for preterm infants (<37 weeks) Fenton growth charts will be applied.

Potential Confounders
To ensure adequate control for confounding, the variables listed below will be considered for the multivariate model . These covariates reflect key determinants of fetal growth and pregnancy outcomes and have been selected based on clinical relevance, expert consensus, and prior literature on pregnancy outcomes in women with IBD : Exposure group, maternal age, history of adverse pregnancy outcomes, type of IBD, history of IBD-related surgery, IBD activity at conception, IBD activity during pregnancy (any trimester), baseline BMI category, weight gain during pregnancy, substance of abuse use, baby sex.

Data Sources: DUMBO is an ongoing, prospective, multicenter observational registry that enrolls pregnant women with IBD at 62 participating centres across Spain. Recruitment began in April 2019 and ended in April 2024 for enrollment; data collection for this analysis will document available data from May 2019 to November 2025. Study investigators are responsible for data collection; each live birth is registered with birth details and neonatal outcomes. Data are collected using REDCap hosted by the Asociación Española de Gastroenterología. Trimesters are classified as first (0-13+6 weeks), second (14-27+6 weeks), and third (28 weeks to delivery).

Study Size: All eligible women enrolled who meet inclusion and do not meet exclusion criteria will be included. The study is expected to include approximately 100 women exposed to ustekinumab, 330 women exposed to anti-TNFα, 250 women exposed to immunomodulators (including corticosteroids), and 380 women with IBD not exposed to any biologic or immunomodulators during pregnancy.

Data Analysis:

Descriptive Analysis: Baseline characteristics of mothers of live-born infants will be described for each exposure group using means and standard deviations (SD) or medians and interquartile ranges (IQR) for continuous variables, and frequencies (%) for categorical variables. Comparison of baseline characteristics between exposure groups will be performed to characterize differences before weighting.

Statistical Methods: The report will include descriptive data of the number of mothers of life-born infants who have entered the study in each of the treatment cohorts, trimester of exposure and counts and proportion of infants with SGA tabulated by exposure status at cohort entry.

Univariate Analysis: The associations between maternal characteristics and SGA will be assessed by univariate analysis using a wide set of variables across IBD characteristics, comorbidities, IBD treatments,

substance of abuse use, obstetric history, anthropometrics, delivery outcomes, maternal hospitalization and surgery, and neonatal variables.

Multivariate analysis: A propensity score for receiving the cohort-defining treatment will be estimated using the main baseline variables expected to influence both treatment assignment and outcomes. To minimize confounding by indication, and only if the number of outcomes allows, IPTW weights derived from this propensity score will be applied in the multivariable analysis to achieve covariate balance between groups. After calculating the IPTW, a multivariable regression model will be fitted; the number of covariates included in the regression model will be limited to approximately one variable for every 10 outcome events, in order to minimize the risk of model overfitting, ensure adequate statistical power, and improve the stability and interpretability of the estimated effect sizes. The treatment group variable will be modelled as a four-category exposure, with ustekinumab as the reference group. If the number of outcome events is insufficient to support the planned analyses, only the multivariable regression model will be performed.

Milestones

Milestone	**Planned date**
Start of patients' follow-up	April 2019
End of patients' follow-up	July 2025
Final report of study results	February 2026

5. AMENDMENTS AND UPDATES

Not applicable.

6. MILESTONES

The planned dates for key milestones in this study are outlined in Table 2.

Table 1: Study Milestones

Milestone:	Planned Date:
Start of patients' follow-up	April 2019
End of patients' follow-up	July 2025
Registration in the EU PAS register	Not registered
Final report of study results	January 2026

7. RATIONALE AND BACKGROUND

Inflammatory bowel disease (IBD) predominantly affects individuals during their reproductive years, with an increasing number of pregnant women being treated with biologic therapies. Among these agents, ustekinumab, an IgG1 monoclonal antibody targeting the p40 subunit of IL-12/23, is increasingly used in patients with either Crohn's disease (CD) or ulcerative colitis (UC). Due to its immunoglobulin structure, ustekinumab can cross the placenta via the neonatal Fc receptor (FcRn), leading to in utero fetal exposure, particularly during the second and third trimesters (Palmeira 2012, Mitrova 2021).

Despite this potential for fetal drug exposure, there is a need for broader real-world data on pregnancy and neonatal outcomes associated with ustekinumab use (Chugh 2024, Odufalu 2022, Mao 2019). Until recently, no adverse pregnancy outcomes had been identified in association with ustekinumab exposure (Wils 2021, Mitrova 2022, Avni-Biron 2022, Mahadevan 2022). However, a recent study (Meyer 2025) raised concerns about a possible increased risk of infants being born small for gestational age (SGA) in women with IBD exposed to ustekinumab during pregnancy when compared to women exposed to anti-tumor necrosis factor (TNFα). Nevertheless, several important limitations in that study must be highlighted: it is based on a retrospective administrative claims-based database (EPI-MERES), where IBD activity and residual confounding -especially from disease severity and corticosteroid use- may not be fully captured; exposure misclassification is possible, given the reliance on dispensing records and assumptions about pharmacologic persistence; the study cohort, though large, lacks detailed clinical data, particularly regarding maternal nutritional status, BMI, smoking, and pregnancy-specific factors that influence fetal growth; timing of exposure (first vs. second/third trimester) is not granularly analyzed in relation to fetal growth windows; there may be immortal-time bias, despite the use of time-dependent exposure modelling; finally, outcome ascertainment (SGA) may be influenced by heterogeneity in growth reference standards and coding practices across hospitals. This study aims to address these gaps and limitations by leveraging prospectively collected clinical data to explore the risk of SGA associated with ustekinumab exposure in a real-world IBD pregnancy cohort.

8. RESEARCH QUESTION AND OBJECTIVES

Research Question

In pregnant women with IBD, is exposure to ustekinumab during pregnancy associated with an increased risk of delivering small for gestational age (SGA) infants compared with exposure to anti-TNFα agents (primary comparator), and compared with exposure to immunomodulators or no immunomodulatory/biologic therapy (secondary comparators), after adjusting for disease activity and other confounders?

Objective(s) and Outcome(s)/Measure(s) of Interest

The objective of the study is to compare the incidence rates of SGA infants born to women with IBD exposed to ustekinumab (including biosimilars) during pregnancy to those exposed to anti-TNFα agents (infliximab, adalimumab, golimumab, including biosimilars), to those exposed to

immunomodulators (including corticosteroids) and to those not exposed to either biologics or immunomodulators. Refer to Section 9.7 for statistical aspects of outcomes or measures of interest.

Hypothesis

There is no clinically meaningful increased risk of SGA in children born to women with IBD who were treated with ustekinumab during pregnancy when compared with the risk in a similar patient population treated with anti-TNFα or no biological treatment.

9. RESEARCH METHODS

9.1. Study Design

The study follows an observational design, based on an analysis of data extracted from the DUMBO registry, a prospective Spanish cohort of pregnant women with IBD (ClinicalTrials.gov ID: NCT03894228) supported by the Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU). The registry prospectively collects clinical, treatment, and outcome data (Figure 1). Only data available from clinical practice were collected. Refer to Section 9.4 for details on the DUMBO registry.

This is a non-interventional study based on secondary use of registry data collected for other purposes. No administration of any therapeutic or prophylactic agent is mandated in this protocol.

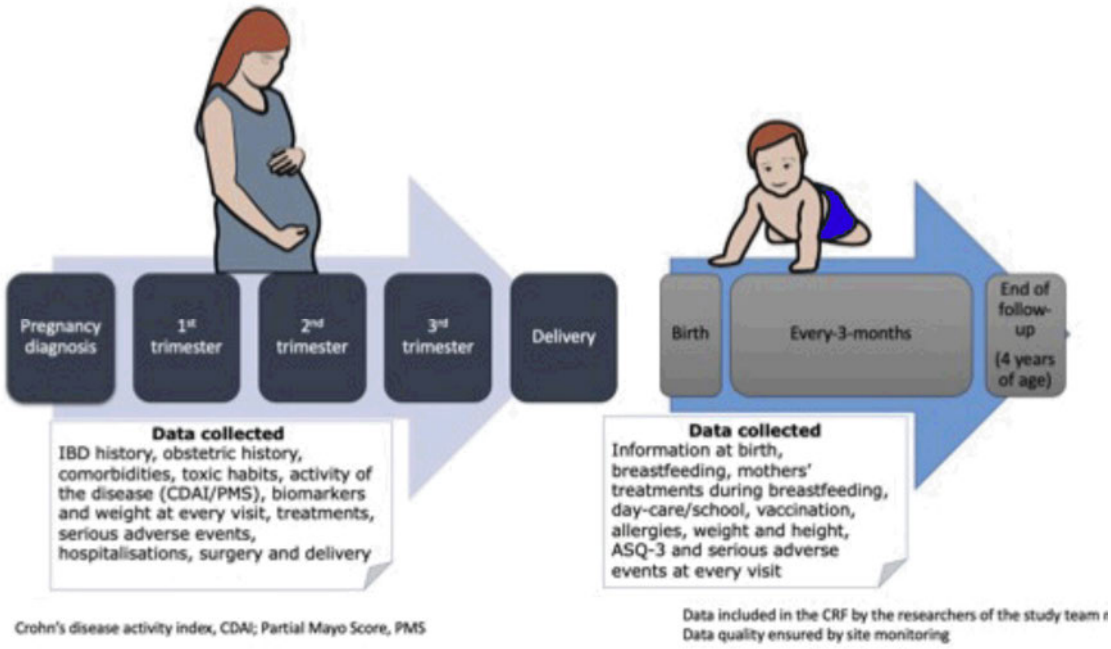

Figure 1 : Summary of DUMBO Registry Protocol

9.2. Setting and Study Population

9.2.1. Study Setting

Data will be drawn from the DUMBO (Safety Of IB(D) Dr(U)gs During Pregnancy And Breastfeeding (M)others And (B)abies' (O)utcomes) registry database. Further details of the data source are provided in Section 9.1.

9.2.2. Patient Selection Criteria

9.2.2.1. Inclusion Criteria

The population under study will consist of women meeting the following criteria:

- Pregnant women with confirmed IBD (CD, UC, IBD-U) recruited into the DUMBO registry before week 28 of gestation.
- Exposed to mesalazine, immunomodulators including corticosteroids, anti-TNFα agents, ustekinumab or not exposed to any treatment at any time during pregnancy or 3 months prior to conception;

9.2.2.2. Exclusion Criteria

Women who meet any of the following criteria will not be eligible for this study:

- Patients exposed to known teratogens from conception through the first trimester of pregnancy (Gomes 2021).
- Patients exposed to targeted small molecules (eg. JAKi, S1P modulators), or biologics other than anti-TNFα agents or ustekinumab
- Lack of informed consent, or loss to follow-up prior to delivery.

9.2.3. Duration of Study Period(s) and Follow-Up

Maternal demographic and clinical data are collected, where available, at baseline (visit 0), defined as the time of study enrolment (after confirmation of pregnancy but before the end of the second trimester). The exposure start date for treatments of interest is defined as the date of first administration of each specific treatment or the date of the last menstrual period if the patient was already under the treatment.

The data collection period will document data available from April 2019 to July 2025.

9.3. Variables

9.3.1. Baseline Information

Maternal demographic and clinical data (disease characteristics, activity and treatment) will be extracted for patients eligible for the study. Number and percentage of multiple pregnancies will

be reported in each group. These variables include but are not limited to the following: IBD Characteristics (Type of IBD, age at diagnosis, IBD activity and severity based on the Crohn's Disease Activity Index [CDAI] in the case of Crohn's disease or the Partial Mayo Score in the case of ulcerative colitis, at conception), comorbidities, IBD treatments, substance of abuse use at conception (alcohol, tobacco, others), obstetric history, anthropometric data.

9.3.2. Exposure

Drugs will be identified at the ingredient level. Exposure groups are defined as :
- Group 1 : Mesalazine or no treatment-exposed cohort: includes children born to mothers treated with mesalazine only, at any time during pregnancy or 3 months prior to conception; or treated with neither biological nor immunomodulatory agents at any time during pregnancy and in the 3 months prior to conception.
- Group 2: Immunomodulators-exposed cohort: includes children born to mothers treated with immunomodulatory agents including corticosteroids, at any time during pregnancy or the 3 months prior to conception;
- Group 3: Anti-TNFα-exposed cohort: children born to mothers treated with anti-TNFα agents (including biosimilars, with or without immunomodulatory agents) at any time during pregnancy or the 3 months prior to conception;
- Group 4: Ustekinumab-exposed cohort: children born to mothers treated with ustekinumab (including biosimilars, with or without immunomodulatory agents) at any time during pregnancy or the 3 months prior to conception;
Biosimilars: No differentiation will be made between original biologics and biosimilars.

9.3.3. Outcomes

Primary outcome definition: Definition of SGA and rationale for scale selection.

In this study, SGA will be defined as birth weight below the 10th percentile for gestational age and sex, in line with the criteria proposed by the World Health Organization (WHO) (de Onis 1996) and used in recent safety studies. This definition allows for harmonization with international research and facilitates comparison with published literature, including pharmacovigilance data relevant for regulatory authorities.

Given the lack of a single universally accepted definition of SGA and the known variability between growth standards, an extensive review of the literature and national consensus guidelines was conducted, as well as consultation with neonatologists and pediatric endocrinologists. After evaluating the available options, the following strategy was adopted:

- For term newborns (≥37 weeks of gestation), the WHO growth standards will be used, applying the 10th percentile cutoff based on sex-specific reference charts (de Onis 1996). These standards are widely accepted and do not require correction for gestational age.

- For preterm infants (<37 weeks), the Fenton growth charts (Fenton 2013), which are the most frequently used and validated references for preterm populations, will be used. These charts provide sex- and gestational age-specific percentiles starting from 22 weeks of gestation and are designed for use at birth without requiring age correction.

Ultimately, the choice to apply the $<10^{th}$ percentile of birth weight using WHO standards for term infants and Fenton charts for preterm infants reflects a balance between:

- Scientific validity,
- Clinical applicability,
- Alignment with regulatory guidance, and
- Consistency with the published literature that triggered this safety assessment.

This approach ensures methodological coherence and facilitates both comparability and interpretability of results in the context of biologic therapy safety during pregnancy.

9.3.4. Potential Confounders

To ensure adequate control for confounding, the variables listed below will be considered for the multivariate model . These covariates have been selected based on clinical relevance, expert consensus, and prior literature on pregnancy outcomes in women with IBD.

1. Exposure group (ustekinumab vs. comparators)
2. Maternal age (continuous)
3. History of adverse pregnancy outcomes (e.g., miscarriage, preterm birth, fetal loss)
4. Type of IBD (CD vs. UC)
5. History of IBD-related surgery (yes/no)
6. IBD activity at conception (remission vs. active disease)
7. IBD activity during pregnancy (any trimester)
8. Baseline BMI category (underweight/ normal /overweight /obese)
9. Weight gain during pregnancy
10. Tobacco use at conception (yes/no)
11. Tobacco use during pregnancy (yes/no)
12. Alcohol use at conception (yes/no and/or g/day if available)
13. Alcohol use during pregnancy (yes/no and/or g/day if available)
14. Baby sex

These variables reflect key determinants of fetal growth and pregnancy outcomes, such as maternal health status, disease control, and exposure to known teratogens or growth-restricting agents.

9.3.5. Other Definitions

1. Disease location and phenotype: IBD location and phenotype will be defined according to the Montreal classification.

2. Date of conception: It will be defined as the date of last menstruation before becoming pregnant.

3. Smoking status at conception: Smoking status will be categorized as "non-smoker" and "smoker", and will be considered at the time of conception. Patients will be considered :

- "smokers" if they smoked more than 7 cigarettes per week for at least 6 months prior to conception.
- "non-smokers" if they never smoked.

4. Diagnosis of pregnancy: Elevated human chorionic gonadotropin hormone in blood or urine (biochemical pregnancy).

5. Comorbidities: Mother's diseases, with special mention to hypertension, diabetes mellitus, seizure disorders, thyroid disorders, allergic disorders, heart diseases, connective tissue diseases, autoimmune diseases, hepatitis.

6. Treatments: Treatments received by the mother in the 3 months before conception and during pregnancy.

7. Normal weight gain during pregnancy is defined according to body mass index (BMI) before pregnancy (Vila-Candel 2021). In mothers with low BMI (<18.5 kg/m2), normal BMI (18.5-24.9 kg/m2), overweight (25-29.9 kg/m2) or obese (≥30 kg/m2) before pregnancy, normal weight gain for a single pregnancy is defined as 13-18 kg, 11-16 kg, 7-11 kg and 5-9 kg, respectively. For twin pregnancies, normal weight gain is 17-25 kg in mothers with low or normal pre-pregnancy BMI, 14-23 kg in mothers who are overweight and 11-19 kg in those who are obese.

8. Preterm delivery: delivery before week 37 of gestation.

9. Low birth weight in term newborns: <2,500 mg.

10. IBD activity: the IBD activity is assessed at conception and in each trimester of gestation based on the CDAI for CD and Partial Mayo Score for UC patients.

11. Low Apgar score: Apgar scores lower than 7 are considered low, and scores of 7 or higher are considered normal at ten minutes after birth.

9.4. Data Sources

DUMBO (NCT03894228) is an ongoing, prospective, multicenter, observational registry study that enrolls pregnant women with IBD (either CD, UC or unclassified IBD [IBD-U]) over a 5-year period at 62 centres across Spain. The DUMBO registry is supported by Grupo Español de Trabajo en Enfermedad de Crohn y Colitis Ulcerosa (GETECCU) and includes women with IBD whose pregnancy was known to the investigator before the 28th week of gestation.
Recruitment began in April 2019 and ended in April 2024. Registration of the patient and obtaining patient permission is performed by the IBD specialists at each participating centre. Study investigators are responsible for data collection. Each incident gestation is followed up through pregnancy and during the first 4 years of the child's life. Treatment and any other interventions

are decided independently by the treating physician and according to local clinical practice. (Chaparro 2021, Palomino 2025).
Trimesters of gestation are classified based on International Classification of Diseases, 10th Revision: first trimester (0-13+6 weeks), second trimester (14-27+6 weeks), and third trimester (28 weeks to delivery).

9.5. Study Size

All eligible women enrolled in the registry who meet the predefined inclusion criteria and do not meet any exclusion criteria will be included in the analysis. The study is expected to include approximately 100 women with IBD exposed to ustekinumab during pregnancy, approximately 330 women with IBD exposed to anti-TNFα during pregnancy, 250 women exposed to immunomodulators (including corticosteroids) and 380 women with IBD not exposed to any biologic or immunomodulators during pregnancy.

Background rates of SGA in children born to women with IBD have been estimated to 10.6% for women exposed to anti-TNFα (Meyer 2025), and ranged from 4.1 to 11.1% in women exposed to immunomodulators or not exposed to biologics and/or IMM (Hoffmann 2022, Meyer 2020) in European cohorts.
- With 100 women exposed to ustekinumab and 330 patients exposed to anti-TNFα, a 10.6% reported SGA rate in children born to women with IBD exposed to anti-TNFα during pregnancy, and considering 80% power (two-sided α=0.05), the minimum detectable OR is **2.57** or higher.
- With 100 women exposed to ustekinumab and 250 exposed to immunomodulators, a 4.1% to 11.1% reported SGA rate in children born to women not exposed to biologics during pregnancy, and considering 80% power (two-sided α=0.05), the minimum detectable OR ranges **between 4 and 2.7** or higher.
- With 100 women exposed to ustekinumab and 380 not exposed to biologics or immunomodulators, a 4.1 to 11.1% reported SGA rate in children born to women with IBD not exposed to biologics during pregnancy, and considering 80% power (two-sided α=0.05), the minimum detectable OR ranges **between 3.75 and 2.57** or higher.

9.6. Data Collection and Management

Maternal demographic and clinical data (disease characteristics, activity and treatment) were collected in DUMBO at baseline (visit 0), defined as the time of study enrolment (after confirmation of pregnancy but before the end of the second trimester). At the end of each trimester and 1 month after delivery (visits 1-4) the following data are collected: disease activity; treatment(s); and SAEs during pregnancy and delivery. All data were collected prospectively. In cases where the end of first trimester precedes study enrolment, disease activity is collected retrospectively. Each live birth is registered in the database as a case at visit 4 (1 month after delivery), and the following clinical information is recorded: Date of birth; sex; birth weight; Apgar score at 5 min and 10 min; vaccinations; and SAEs. All study data are collected by the IBD specialists using the electronic data capture software tool REDCap (Research Electronic Data

Capture; Vanderbilt University, Nashville, TN, USA), which is hosted by the Asociación Española de Gastroenterología (AEG, Madrid, Spain), a not-for-profit medical society (Chaparro 2021).

9.7. Data Analysis

A description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections.

9.7.1. Descriptive Analysis

9.7.1.1. Baseline Characteristics (at visit 0)

Baseline characteristics of mothers of live-born infants will be described for each exposure group using means and standard deviations (SD) or medians and interquartile range (IQR) for continuous variables, and frequencies (%) for categorical variables.

Comparison of baseline characteristics between exposure groups will be performed to characterize differences before weighting using :

- Student's t-test or Mann-Whitney U test for normally and non-normally distributed continuous variables, respectively.
- Chi-square or Fisher's exact test for categorical variables.

9.7.2. Statistical Methods

The report will include data on the number of mothers of life-born infants who have entered the study in each of the treatment cohorts, trimester of exposure and counts and proportion of infants with SGA tabulated by exposure status at cohort entry.

9.7.2.1. Model Specification

9.7.2.1.1. Univariate Analysis

Associations between (expecting) mother characteristics and SGA will be assessed by univariate analysis.

- Crude rates of SGA will be calculated for each exposure group.
- Odds ratios and 95% confidence intervals will be estimated using logistic regression.

The following variables will be considered for univariate analysis, grouped by thematic domain:

1. IBD Characteristics for (expecting) mothers

- Type of IBD (Crohn's disease [CD] / Ulcerative colitis [UC])
- Mother age at IBD diagnosis
- Mother age at conception
- Montreal classification (CD: A1/A2/A3, L1/L2/L3, B1/B2/B3)
- Upper GI tract involvement
- Perianal disease
- Montreal classification (UC: E1/E2/E3)

- IBD activity at conception (remission, mild/moderate/severe for CD and UC)
- IBD activity during pregnancy (any of the 3 visits, see section 9.6; same categories as above)
- Hemoglobin and CRP during pregnancy (mean or median values)
- Hemoglobin (categorical: no anemia /anemia /severe anemia)

2. Comorbidities

- Hypertension
- Diabetes mellitus
- Seizures
- Thyroid disease
- Allergies
- Heart disease
- Immune-mediated diseases
- Other comorbidities

3. IBD treatment and exposure

- Biologic treatment group definition (ustekinumab, anti-TNFα, etc.)
- Treatment discontinuation before delivery
- Reason for discontinuation: sustained remission, IBD activity, adverse events, other
- Duration of treatment exposure during pregnancy
- Intensified regimen (yes/no)

4. Concomitant IBD therapies

5. Substance of abuse use

- Substance of abuse use at conception (alcohol, tobacco, others; daily quantity)
- Substance of abuse use during pregnancy (same items as above)

6. Obstetric history

- Previous pregnancies
- Outcomes of previous pregnancies (e.g., miscarriage, ectopic, molar, preterm, etc.)
- Maternal age at conception
- IBD duration at conception (years)
- Natural conception vs. fertility treatment
- Fetal heartbeat at first ultrasound
- Number of fetuses per patient
- Pathological findings on prenatal ultrasound

7. Anthropometric data

- Pre-pregnancy BMI (underweight, normal weight, overweight, obesity)
- Maternal weight gain during pregnancy (below/within/above guidelines)

8. Delivery outcomes

- Gestational age at delivery (weeks)
- Type of delivery (spontaneous vaginal, instrumental, cesarean)

- Main indications for cesarean delivery
- Complications from instrumental delivery

10. Maternal hospitalization and surgery

- Number and duration of hospital admissions
- ICU admission
- Surgeries related to IBD or other causes

The following variables will also be tested in the univariate analysis for descriptive purposes :

12. Neonatal Variables

- Sex (female)
- Birth weight and length
- Gestational age at birth
- Apgar scores at 1 and 5 minutes
- Prematurity

9.7.2.1.2. Multivariate Analysis

A propensity score for receiving the cohort-defining treatment will be estimated using the main baseline variables expected to influence both treatment assignment and outcomes (listed in Section 9.3.4). To minimize confounding by indication, and only if the number of outcomes allows, IPTW weights derived from this propensity score will be applied in the multivariable analysis to achieve covariate balance between groups. After calculating the IPTW, a multivariable regression model will be fitted; the number of covariates included in the model will be limited to approximately one variable for every 10 outcome events, in order to minimize the risk of model overfitting, ensure adequate statistical power, and improve the stability and interpretability of the estimated effect sizes. For the IPTW analysis, no trimming of extreme weights will be performed, and no patients will be excluded. Covariate balance before and after weighting will be assessed using standardized mean differences (with $|SMD|<0.1$ indicating acceptable balance) and graphical diagnostics (love plots). The weight distribution (median, IQR, maximum), the number of extreme weights, and the effective sample size will also be reported. The treatment group variable will be modelled as a four-category exposure, with ustekinumab as the reference group. This will allow estimation of the odds ratio for the risk of SGA in comparison with each of the other treatment groups, separately.
If the number of outcome events is insufficient to support the planned analyses, only the multivariable regression model will be performed.

9.7.1. Missing Values

No imputation will be performed for missing values in the primary outcome variable (SGA). This variable will be analyzed and reported based on observed data only.

9.8. Quality Control

9.8.1. Quality Assurance and Quality Control of the Registry

Standard operating procedures or internal process guidance at each research center and/or coordinating center should be adhered to for the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and any other relevant process documents related to data transfer and data pooling.

9.9. Strengths and Limitations of the Research Methods

The DUMBO registry (Chaparro 2021) offers several strengths that make it well suited for evaluating the risk of SGA following exposure to ustekinumab during pregnancy. It features a prospective design with systematic follow-up of both mothers and their children up to four years postpartum, ensuring comprehensive longitudinal data. The registry includes detailed records of drug exposure, including ustekinumab and other biologics, with precise timing relative to conception and gestation. It collects granular obstetric information, such as birth weight, gestational age, Apgar scores, and small for gestational age (SGA). Outcomes are defined using structured and standardized criteria, reducing heterogeneity and minimizing reporting bias. Its national multicenter participation enhances the representativeness and external validity of the findings. The use of validated electronic data capture tools (REDCap) ensures standardized, secure, and high-quality data collection. Additionally, the registry undergoes remote monitoring of 100% of the entered data, along with on-site monitoring of a selected proportion, further ensuring data accuracy and integrity.

Limitations inherent to the use of a registry for epidemiological research are applicable to this study. The proposed study has inherent limitations related to its design and the secondary use of registry data: Because patient enrollment can occur after the last menstrual period, the registry may lack information from the pre-enrollment period. Additionally, analyses are constrained by the predefined set of variables collected in the DUMBO registry. Missing data is expected to be negligeable.

10. PROTECTION OF HUMAN SUBJECTS

The study was approved by the Ethics Committee for Research with Medicines of Hospital Universitario de La Princesa (Spain) and is being conducted in accordance with the Declaration of Helsinki (2013 version) and current Spanish legislation. Patients provided written informed consent to participate in the study, in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, and with local legal and administrative regulations (Chaparro 2021)

11. COLLECTION AND REPORTING OF SAFETY DATA

This study is a non-interventional study based on the DUMBO registry and uses data that already exist in this registry database. It is designed to assess the relation between ustekinumab exposure during pregnancy and risk of SGA based on aggregate analysis.

Data from the registry will be provided to the sponsor in the form of aggregate safety data tables only. Based on the format of the data provided, it is not possible to link a particular product and medical event for any identifiable individual. Thus, it will not be possible to identify any adverse drug reactions. The study results will be assessed for medically important results.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the investigators. Patient identifiers will not be used in the publication of results. The sponsor will register and/or disclose the existence of and the results of the study as required by law.

13. REFERENCES

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6. Mahadevan U, Naureckas S, Tikhonov I, et al. Pregnancy outcomes following periconceptional or gestational exposure to ustekinumab: review of cases reported to the manufacturer's global safety database. Aliment Pharmacol Ther 2022;56:477–490.
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10. Vila-Candel R, Faus Garcia M, Martin-Moreno JM. Standard international recommendations for gestational weight gain: suitability for our population. Nutr Hosp 2021;38:306–314.
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14. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

14.1. Annex 1.1: List of Standalone Documents

None

15. ADDITIONAL INFORMATION

None.

16. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Study title: Ustekinumab and risk of small for gestational age in inflammatory bowel disease pregnancies: data from the DUMBO registry

EU PAS Register® number:
Study reference number (if applicable): PCSIMMA0309

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

Comments:

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)	☒	☐	☐	Section 7
2.1.2 The objective(s) of the study?	☒	☐	☐	Section 8
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	Section 8
2.1.4 Which hypothesis(-es) is (are) to be tested?	☒	☐	☐	Section 8
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

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)	☒	☐	☐	Section 9.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	Section 9.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	Section 9.7

[a] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[b] Date from which the analytical dataset is completely available.

Section 3: Study design		Yes	No	N/A	Section Number
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))	☒	☐	☐	Section 9.7.2
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)	☒	☐	☐	Section 11

Comments:

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

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)	☒	☐	☐	Section 9.3.2
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☐	☒	
5.3	Is exposure categorised according to time windows?	☒	☐	☐	Section 9.3.2
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	Section 9.7.2
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	Section 9.3.2
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	Section 9.3.2

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?	☒	☐	☐	Section 9.3.3

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	Section 9.3.3
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)	☐	☐	☒	
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)	☐	☐	☒	

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)	☒	☐	☐	Section 9.7.2
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☐	☒	
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☐	☐	☒	

Comments:

Selection and information bias are expected to be minimal

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)	☒	☐	☐	Section 9.7.2

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)	☒	☐	☐	Section 9.6
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	Section 9.6
9.1.3 Covariates and other characteristics?	☒	☐	☐	Section 9.6
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)	☒	☐	☐	Section 9.3

Section 9: Data sources	Yes	No	N/A	Section Number
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	Section 9.3
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	Section 9.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☐	☐	☒	
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☐	☒	
9.3.3 Covariates and other characteristics?	☐	☐	☒	
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	Section 9.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	Section 9.5
10.3 Are descriptive analyses included?	☒	☐	☐	Section 9.7.1
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	Section 9.7.2.1.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☐	☒	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	Section 9.7.1
10.8 Are relevant sensitivity analyses described?	☐	☒	☐	

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)	☒	☐	☐	Section 9.6
11.2 Are methods of quality assurance described?	☒	☐	☐	Section 9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1.1 Selection bias? 12.1.2 Information bias? 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).	☐ ☐ ☐	☐ ☐ ☐	☒ ☒ ☒	
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)	☒	☐	☐	Section 9.5

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?	☒	☐	☐	Section 10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	Section 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?	☐	☐	☒	

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)?	☒	☐	☐	Section 12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	Section 12

Comments:

SPONSOR'S RESPONSIBLE PARTY SIGNATURE AND PARTICIPATING PHYSICIAN AGREEMENT

Sponsor's Responsible Party (Main Author):

Name (typed or printed): _____

Institution: _____

Signature: _____ Date: _____

Participating Physician Agreement:

I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the conduct of the study and the obligations of confidentiality.

Coordinating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Signature: _____ Date: _____

(Day Month Year)

Principal Participating Physician:

Name (typed or printed): _____

Institution and Address: _____

_____

_____

Telephone Number: _____

Signature: _____ Date: _____

(Day Month Year)

Note: If the address or telephone number of the participating physician changes during the study, written notification will be provided to the sponsor; a protocol amendment will not be required.