Safety of IL-17 and IL-23 inhibitors as treatment for immune mediated inflammatory diseases at conception and during pregnancy: an ENTIS study.

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1. INTRODUCTION AND RATIONALE

Immune mediated inflammatory diseases (IMIDs) comprises a relatively common group of conditions (5-7% in the Western population), characterized by dysregulation of the immune system leading to acute or chronic inflammation that can affect any organ system (1). Currently, interleukin (IL)-17 inhibitors (secukinumab, ixekizumab, bimekizumab, brodalumab), IL-23 inhibitors (guselkumab, mirikizumab, risankizumab, tildrakizumab), and IL-12/23 inhibitors (ustekinumab) are increasingly used to treat IMIDs like psoriasis, psoriatic arthritis (PsA), axial spondylitis (AS) and inflammatory bowel disease (IBD). The onset of most IMIDs peaks during reproductive age, posing significant challenges in the treatment of these conditions during conception and pregnancy. IMID disease flares during pregnancy have been associated with adverse pregnancy outcomes (2-4). Additionally, IMIDs might affect male reproductive health (5). This underscores the importance of maintaining disease control at conception and throughout pregnancy.

IL-17, IL-23, and IL-12/23 inhibitors are human immunoglobulin G (IgG) molecules, which are actively transferred across the placenta through neonatal Fc receptors (FcRn). This placental transfer starts around the 13th week of gestation and increases after the 20th week. Therefore, it is proposed that the use of biologics during the critical period of early embryogenesis is associated with a low risk of teratogenic effects. However, the progressive increase in fetal exposure during the second and third trimesters may potentially impact fetal development, lead to immunomodulation or latered immune responses in the newborn, including effects on susceptibility to infections or responses to early-life vaccinations (6).

Previous studies and case reports reported on maternal secukinumab (7, 8), ixekizumab (8, 9), tildrakizumab (8, 10) and ustekinumab (8, 11-20) exposure during pregnancy (see also Appendix 1). Only a few studies reported on paternal use of secukinumab (7), ixekizumab (9), and ustekinumab (21) during spermatogenesis. Paternal use of these medications may impact pregnancy outcomes via (epi)genetic changes in sperm or immunological changes in the composition of seminal plasma (21, 22).

Overall, most studies report no increased risk on adverse pregnancy outcomes following IL-17, IL-23, or IL-12/23 exposure. Although evidence regarding the IL-12/23 inhibitor ustekinumab is increasing, data on IL-17 and IL-23 inhibitors remain limited. Current treatment guidelines generally advise against the use of IL-17, IL-23, and IL-12/23 inhibitors during pregnancy due to insufficient safety data (23-26).

As a result, clinicians face difficult therapeutic decisions when treating patients with IMIDs who are planning to conceive or are pregnant. Discontinuation of effective therapy may increase the risk of disease flare, depending on disease type, which itself can negatively impact maternal and fetal health.

If deemed necessary to control disease, maternal use of IL-17, or IL-23 or IL-12/23 inhibitors may be considered during the first trimester under an individualized benefit/risk assessment. For male patients it is suggested that they may continue biologic therapies when planning conception (23-26).

This study aims to contribute to data regarding the safety of maternal and paternal exposure of these biologics.

2. OBJECTIVES

Maternal exposures:
The primary aim of this study is to evaluate the risk of adverse pregnancy outcomes (spontaneous abortion, stillbirth, pregnancy termination), pregnancy complications (preeclampsia, gestational hypertension, gestational diabetes, and premature rupture of membranes [PROM]), and adverse neonatal outcomes (major birth defects, small for gestational age, low birth weight, preterm birth, infections) after maternal exposure to IL-17, IL-23, IL-2/23 inhibitors at conception and/or during pregnancy in the etiologically relevant time period for the outcome of interest.

Secondly, to provide more information directly relevant to clinical practice, we will stratify the primary analyses by underlying disease for which the IL-17, IL-23 or IL-12/23 inhibitor is prescribed (i.e. psoriasis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and axial spondyloarthritis) to explore potential confounding by indication. Additionally, if the number of exposures allows, the results will be stratified per biologic type.

Paternal exposures:
In this study we aim to evaluate the risk of adverse pregnancy outcomes (spontaneous abortion, stillbirth, pregnancy termination), and adverse neonatal outcomes (major birth defects, small for gestational age, low birth weight, preterm birth,) after paternal exposure to IL-17, IL-23, IL-12/23 inhibitors at conception.

3. STUDY DESIGN

This study is a multinational cohort study utilizing multiple databases comprising prospectively collected cases and reference populations.

Study period
Data until January 2026 will be collected, with an estimated delivery date cut off of October 1, 2025.

Exposed group

- Treatment with IL-17, IL-23 or IL-12/23 inhibitor: bimekizumab, brodalumab, guselkumab, ixekizumab, mirikizumab, risankizumab, secukinumab, tildrakizumab, ustekinumab (independent of the indication for which the drug is prescribed).
    - Maternal exposure: at least 3 months before date of LMP and/or during pregnancy.
    - Paternal exposure: at least 3 months before conception.

  Exposure is considered to occur if the time from one injection to the subsequent injection, according to the standard intervals for that specific interleukin inhibitor, falls within the period of interest.
- Type of IL-17, IL-23 or IL-12/23 inhibitor and timing of exposure at least per trimester is known.

Reference group

- For each IL-17, IL-23 or IL-12/23 inhibitor exposed case, at least two patients of the same sex and disease, without maternal or paternal exposure to IL-17, IL-23 or IL-12/23 inhibitors, matched for gestational age at enrolment (+/- two weeks) will be included.

Exclusion criteria

- Lost to follow-up or unknown pregnancy outcomes.
- Maternal exposure at any time in pregnancy to any of the following: retinoids (acitretin, alitretinoin, bexarotene, isotretinoin, tretinoin), any cytotoxic drugs (cisplatin, doxorubicin, methotrexate, thalidomide), the following antiepileptic medication (valproate, carbamazepine, phenytoin, fosphenytoin, primidone, topiramate, phenobarbital), leflunomide, lenalidomide, any coumarin derivatives (dicoumarol, phenindione, warfarin, phenprocoumon, acenocoumarol, fluindione), lithium, misoprostol or mifepristone except exposure for labour induction, carbimazole and methimazole/thiamazole, mycophenolate, accounting for pre-pregnancy exposure by elimination half-life (5 half-lives of the individual medications).
- Exposure during 2nd and 3rd trimester to renin-angiotensin system inhibitors or systemic tetracyclines.
- Exposure to NSAIDs from the 20th week of gestation onward.
- Diagnosis of toxoplasmosis, cytomegalovirus, parvovirus b19, rubella, or zika during pregnancy.
- Malignancies or malignancy related conditions (ICD-10: C00-D09) during pregnancy.
- Multifetal pregnancies.

4. DATA COLLECTION

Data on pregnancy outcomes after maternal or paternal exposure to IL-17, IL-23 or IL-12/23 inhibitors at conception and/or during pregnancy will be requested by all collaborating European Network of Teratology Information Services (ENTIS) centers, PRIDE Study (https://pridestudy.nl/), BELpREG registry (https://belpreg.be/), and BioCAPTURE registry (https://biocapture.nl/?lang=en).
Anonymous data will be sent to coordinating researchers of this project in Radboudumc, Nijmegen, The Netherlands.
Variables that will be collected their definitions are listed in Appendix 2. All data will be combined in one datafile for analysis. A data sheet in which the data can be collected will be provided.

5. EXPECTED SAMPLE SIZE

Based on an inventory of the number of cases at the participating centres, the estimated sample size is as follows:

Prospective maternal exposures:

- IL-17 inhibitors: 100
- IL-23 inhibitors: 46
- IL-12/23 inhibitors: 373

Prospective paternal exposures:

- IL-17 inhibitors: 15
- IL-23 inhibitors: 3
- IL-12/23 inhibitors: 11

See for an overview of the expected cases per biologic type and per TIS centre/registry in Appendix 3.

6. DATA ANALYSIS

Duplicates

Identification of duplicates will be performed using a combination of details, including country of report, exposure year, maternal/paternal age, medication, dosage, duration of exposure, duration of pregnancy, pregnancy and neonatal outcomes. Identified duplicates will be excluded.

Patient and treatment characteristics

Descriptive analyses will be performed to present maternal/paternal characteristics and treatment characteristics.

Pregnancy and neonatal outcomes after maternal exposure

Birth defects will be classified by two independent researchers blinded for the exposure data, according to the European Network of Population-based Registries for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) ICD10-British Paediatric Association system (27). The assessment of major birth defects will be restricted to live births and pregnancy losses with confirmed outcomes after appropriate medical examination. Minor birth defects will not be classified due to the likelihood of underreporting. Descriptive analyses will be performed to show the occurrence of the major birth defects.

To estimate the risk on major birth defects the crude risk will be determined, by dividing the total number of infants or foetuses with birth defects by the sum of all live-born infants, plus the number of cases with known birth defects in stillbirths and terminated pregnancies.

To assess the association between exposure to IL-17, IL-23 or IL-12/23 inhibitors and the risk on pregnancy complications and adverse neonatal outcomes, modified Poisson regression will be applied, yielding relative risks (RR) with 95% confidence intervals (95% CI). This analysis will be adjusted for confounders using propensity score methods. Applicable confounders for each outcome will be identified using Directed Acyclic Graphs (DAG). As an example, the DAG for the outcome spontaneous abortion is presented in Figure 1.

Crude rates for spontaneous abortion and stillbirth will be calculated taking into account the competing risk of induced abortions. Additionally, spontaneous abortion and stillbirth rates will be analysed using an event-history approach (cumulative incidence functions), accounting for the fact that women entered the cohort at varying gestational ages—resulting in left-truncation—and that pregnancy loss, induced abortion, and live birth are competing events. Cases with missing information on gestational age at inclusion or pregnancy outcome will be excluded from the cumulative incidence analysis.

To assess the association between spontaneous abortion, still birth, pregnancy termination and live birth with IL-17, IL-23 or IL12/23 inhibitor exposure using Cox proportional cause specific hazard models, adjusted for the minimally set of confounders and risk factors for these outcomes identified using a DAG.

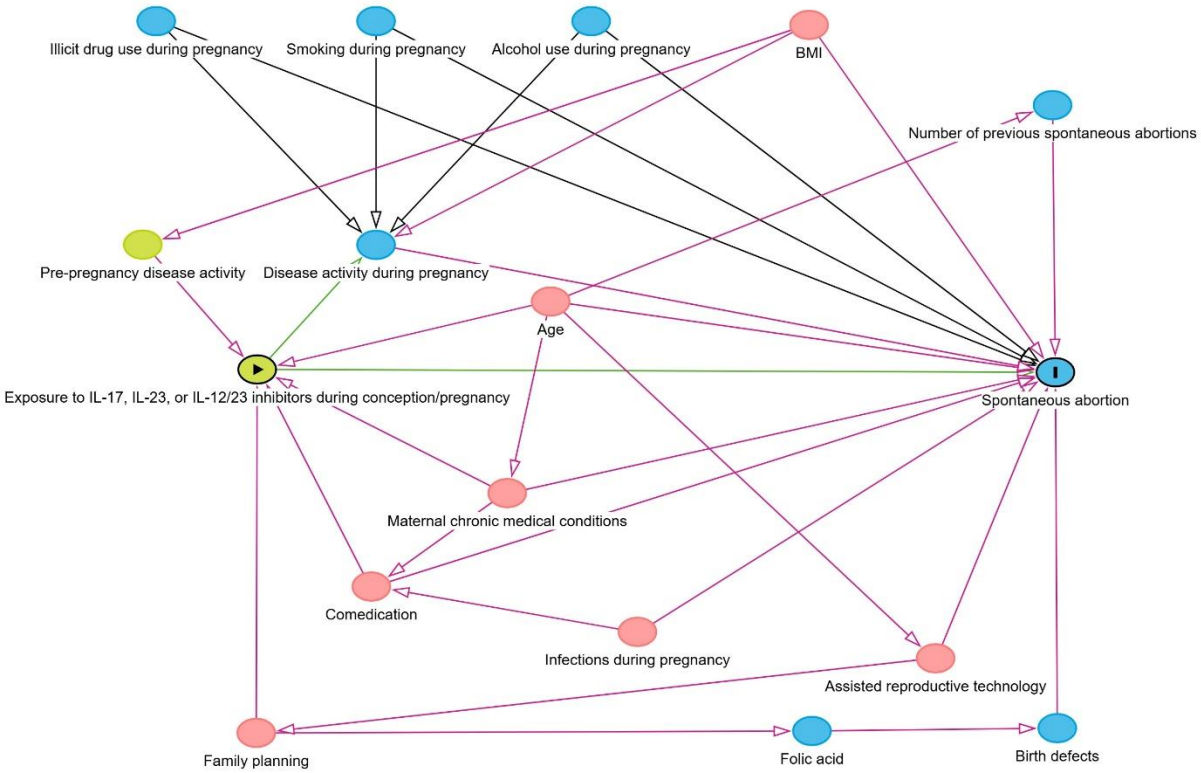

Figure 1| Directed Acyclic Graph (DAG) to assess applicable confounders to adjust for when testing the association between exposure to IL-17, IL-23, IL-12/23 inhibitor during conception/pregnancy and spontaneous abortion.
Example of a minimal sufficient adjustment set: Age, Assisted reproductive technology, BMI, Comedication, Folic acid, Maternal chronic medical conditions

All analyses will be done for IL-17 inhibitors, IL-23 inhibitors and IL-12/23 inhibitors as separate groups. If sample size allows, analyses will be stratified for disease type, IL-17 or IL-23 inhibitor type and timing of exposure.

A sensitivity analysis will be performed to evaluate the exposure definition. In the primary analyses, exposure is defined based on whether the interval between two consecutive injections—according to the standard dosing schedule for the specific interleukin inhibitor—overlaps with the period of interest. In the sensitivity analysis, this definition will be compared with an alternative approach in which exposure is defined by the injection itself being administered during the period of interest.

A graph will be used to visualise the patterns of exposure time and pregnancy.

<u>Pregnancy and neonatal outcomes after paternal exposure</u>
Due to the expected number of cases, paternal exposures will be reported as a case series.

<u>Missing data</u>
Multiple imputation will be used to deal with missing values.

<u>Reporting</u>
This study will be reported according to the STROBE guidelines.

7. CONSENT AND ETHICAL APPROVAL

Each collaborating TIS is responsible for addressing local aspects of ethics and obtaining the required patient consents. For the PRIDE Study, BELpPREG and BioCAPTURE cohort consent is provided by the participants at the moment of inclusion in the study.

8. DATA MANAGEMENT

Data will be shared with the study team (Radboudumc, Nijmegen, The Netherlands), processed and stored in accordance with the terms outlined in the Data Transfer Agreement. A Workspace within the Digital Research Environment (DRE) will be set up for secure data analysis and storage, with authorized access by project members.

9. AUTHORSHIP

All contributors to the study will be co-author when they meet the criteria of the ICMJE guidelines (https://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html). This includes at least the members of the study team and all participating TIS centres. Liana Barenbrug will be listed as first author, Marleen van Gelder will be listed as last author, and Evelin Beck will be listed as a shared last author. The order of all other authors who qualify for authorship will be determined based on the number of cases contributed.

10. STUDY REGISTRATION

The study will be registered as a real-world study in the HMA-EMA catalogue of real-world data studies (https://catalogues.ema.europa.eu/catalogue-rwd-studies).

11. TIME LINE

<table>
<tr><td>May 2025</td><td rowspan="2">Protocol drafting and inventory TIS participation</td></tr>
<tr><td>June 2025</td></tr>
<tr><td>July 2025</td><td rowspan="7">Finalizing protocol</td></tr>
<tr><td>August 2025</td></tr>
<tr><td>September 2025</td></tr>
<tr><td>October 2025</td></tr>
<tr><td>November 2025</td></tr>
<tr><td>December 2025</td></tr>
<tr><td>January 2026</td></tr>
<tr><td>February 2026</td><td rowspan="4">Institutional Review Board / ethical approval, data transfer, review of data and plausibility check,
data pooling, data analysis.</td></tr>
<tr><td>March 2026</td></tr>
<tr><td>April 2026</td></tr>
<tr><td>May 2026</td></tr>
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June 2026	
July 2026	Manuscript preparation
August 2026	
September 2026	Paper submission

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Appendix 1| List of studies reporting on pregnancy outcomes following IL-17, IL-23 or IL-12/23 inhibitors.

- A report of clinical trial and post-marketing data of 292 exposures of ***secukinumab*** in patients with psoriasis, PsA and AxSpa (N=238 maternal exposures (mainly first trimester), N=54 paternal exposures)(7). Risk of pregnancy loss seems to be comparable with the general population. Three congenital abnormalities were reported after maternal exposure and one after paternal exposure.
- A report of clinical trial and post-marketing data of 190 exposures of ***ixekizumab*** in patients with psoriasis, PsA and AxSpa (N=99 maternal exposures (mainly first trimester), N=91 paternal exposures) (9). Risk of pregnancy loss seems to be comparable with the general population. One congenital malformation was found after maternal exposure (congenital malformation and three after paternal exposure.
- A report of clinical trial data of 14 maternal exposures of ***tildrakizumab*** in patients with psoriasis and Crohn's disease and healthy volunteers (10). No congenital malformation or other safety signals (e.g., increased risk for pregnancy loss) was found.
- A report of post-marketing data of 70 maternal exposures of ***ustekinumab*** in patients with psoriasis or PsA (11). One congenital anomaly was reported and pregnancy outcomes were similar to the general population. Data for secukinumab, risankizumab, tildrakizumab, brodalumab, ixekizumab, and guselkumab was also collected in this databases, however, number of exposures is unknown and results were not presented separately from other biologics.
- A report of clinical trial and post-marketing data of 621 maternal exposures of ***ustekinumab*** in patients with psoriasis, PsA or IBD (12). Eleven major congenital malformations were reported and adverse pregnancy outcome rates were comparable with the general population. Rates were also reported for each disease separately.
- A report of clinical trial data of 39 maternal exposures of ***ustekinumab*** in patients with IBD (13). No congenital anomalies were reported and pregnancy outcomes were comparable with the general population.
- A prospective multicenter study (Israel) reported on 27 maternal exposures of ***ustekinumab*** in patients with IBD and included a control group of IBD patients not exposed to ustekinumab (14). This study reported favorable pregnancy and neonatal outcomes compared to IBD patients treated with TNF-a inhibitors or other therapy.
- A prospective multicenter study (Czech Republic) reported on 54 maternal exposures of ***ustekinumab*** in patients with IBD and used a control group of IBD patients exposed to TNF-a inhibitors (15). Three congenital malformations were reported. No statistical difference between the ustekinumab and TNF-a group were found in terms of adverse pregnancy outcomes.
- A study on 464 maternal ***ustekinumab*** exposures in patients with IBD from the EPI-MERES registry (France) showed an increased risk for SGA compared to anti-TNF treatment, but no increased risk for other pregnancy or neonatal complications (16).
- A study of 47 maternal ***ustekinumab*** exposures in patients with IBD from the PIANO registry (USA) reported 10 congenital malformations but showed no increased risk for adverse pregnancy and neonatal outcomes (17).
- A prospective observational multicenter study (Denmark and The Netherlands) reported on 76 maternal exposures to ***ustekinumab*** in patients with IBD (18). Six congenital malformations were reported. No increased risk on pregnancy complications and infections in newborns were found.
- A retrospective cohort study among GETAID centers (France) reported on 29 maternal ***ustekinumab*** exposures showed no increased risk for pregnancy complications compared to TNF-a inhibitor exposure (19).
- A study using the EudraVigilance database reported on 8 ***ixekizumab***, 58 ***secukinumab*** and 286 ***ustekinumab*** maternal exposures, and 23 ixekizumab, 24 secukinumab and 13 ustekinumab paternal exposures (8). The occurrence of congenital malformations was compared to certolizumab exposures. No specific congenital malformation patterns were found.
- In a study using WHO pharmacovigilance data compared the risk on adverse pregnancy outcomes after exposure to ***IL-17 or IL-23 inhibitors*** to exposure of TNF-a inhibitors (20). This study reported a lower reporting odds ratio of adverse pregnancy outcomes for all IL-17 and IL-23 inhibitors compared to TNF-a inhibitors, except for brodalumab. Additionally, risankizumab was reported with a higher frequency of abortion and stillbirth compared to TNF-a inhibitors.
- A study using pharmacy administrative claims data reported on 114 paternal ustekinumab exposures (21). No increased risk for adverse pregnancy outcomes were found compared to non-exposed fathers.

Appendix 2| List of variables to be collected

Item	Definition	Recommended data format and suggested values
Administrative details		
TIS center	Name of the TIS center	
Primary reporter type	Type of reporter providing the information	Values: a) Healthcare professional, b) Other
Gestational age at initial contact	Gestional age at initial contact	Integer
Initial report date	Date when pregnancy is initially reported to the data collection system	Date (dd/mm/yyyy)
Prospective status	Whether the pregnancy was reported prospectively or retrospectively. Pregnancies where considered to be "prospective" when the pregnancy outcome was unknown at the time of the first contact with each TIS.	Values: a) Prospective, b) Retrospective, c) Unknown
Maternal / paternal details		
Maternal age at last menstrual period (LMP)	Mother's age (in years) on the first day of the last menstrual period prior to the pregnancy	Integer
Maternal BMI pre-pregnancy	Maternal BMI at the time of conception (kg/m2)	Integer
Maternal smoking in pregnancy	Maternal smoking of tobacco during pregnancy	Values: a) Yes, b) No c) Unknown
Maternal alcohol in pregnancy	Maternal alcohol consumption during pregnancy	Values: a) Yes, b) No c) Unknown
Maternal illicit drug use in pregnancy	Maternal recreational drug use in pregnancy	Values: a) Yes, b) No c) Unknown
Maternal folic acid use pre-pregnancy	Maternal folic acid use before pregnancy	Values: a) Yes, b) No c) Unknown
Maternal folic acid use during pregnancy	Maternal folic acid use in pregnancy	Values: a) Yes, b) No c) Unknown
Paternal age at conception	In case of paternal exposure. Father's age (in years) on the day of conception.	Integer
Paternal BMI	Paternal BMI at conception	Integer
Pregnancy details		
Date of LMP	Date of the first day of the last menstrual period prior to conception. LMP is derived as EDD-280 days (please note in early pregnancy, the EDD is derived from LMP, whereas in later pregnancy the EDD can be defined from ultrasound fetal crown- rump length measurements) or (where EDD is unknown) the date of end of pregnancy minus the gestational age at end of pregnancy (in days).	Date (dd/mm/yyyy)
Expected date of delivery (EDD)	Expected date of delivery. The directly reported value may have been based on (e.g.) the date of LMP, results from ultra-sound examinations, the date of embryo transfer (assisted fertilisation). Alternatively, it could be derived from entered dates of LMP based on 280 day gestation length (using the LMP date) or 266 day gestation length	Date (dd/mm/yyyy)
Source of directly reported EDD	The final method used to establish the estimated date of delivery. (using estimated date of conception from fetal ultrasound measurements).	Value 1 - Options: a) LMP, b) Date of embryo transfer, c) Ultrasound results, d) Other (detail) - Text
Assisted conception	Assisted conception technique utilized for this pregnancy	Options: a) Yes, b) No, c) Unknown
Prenatal test(s)	Details of any medical prenatal examination or test performed to investigate fetal wellbeing/medical conditions. Values to be reported for each prenatal test performed. Tests to be reported here are only those that have been conducted in a medical setting, social or non-clinical prenatal ultrasound scans should not be described.	Value 1: Date test performed (dd/mm/yyyy) Value 2 (approx. gestational age in days when test was performed): Text Value 3 (Type of prenatal test (see notes): Text : a) Chorionic Villous Biopsy, b) Amniocentesis, c) Cordocentesis, d) 2d USS, e) 4d USS, f) Maternal blood tests, g) Nuchal translucency, h)

		Maternal serum (alpha fetal protein etc.), i) Other Value 4 (Were any congenital anomalies identified) - Options: a) Yes, b) No, c) Unknown If "Yes", Value 5 (Congenital anomaly details/ findings/ diagnosis): Text If "Yes", Value 6 (MedDRA/ICD diagnosis code): Text If "Yes", Value 7 (Coding system) - Options: a) MedDRA, b) ICD10, c) Other (detail) - Text
Maternal and paternal medical history details		
Maternal pre-pregnancy medical conditions (history)	Maternal medical chronic conditions present prior to pregnancy	Value 1 - Options: a) Yes, b) No, c) Unknown If "Yes", a) Asthma b) Cancer c) Cardiovascular disorder d) Chronic hypertension e) Diabetes type 1 or 2 f) Mental or behavioral disorder (e.g., anxiety, depression, ADHD) g) Other autoimmune or inflammatory disease than for which the interleukin inhibitor is prescribed h) Thyroid related disease Other
Paternal pre-pregnancy medical conditions (history)	Paternal medical chronic conditions present prior to pregnancy	Value 1 - Options: a) Yes, b) No, c) Unknown If "Yes", a) Asthma b) Cancer c) Cardiovascular disorder d) Chronic hypertension e) Diabetes type 1 or 2 f) Mental or behavioral disorder (e.g., anxiety, depression, ADHD) g) Other autoimmune or inflammatory disease than for which the interleukin inhibitor is prescribed h) Thyroid related disease i) Other
Number of previous pregnancies	Number of previous pregnancy (including non-live births) experienced by the mother only.	Integer
Number of previous live births	Number of previous live births.	Integer
Number of previous spontaneous abortions	Number of previous spontaneous abortions.	Integer
Number of previous induced terminations	Number of previous induced terminations (for any reason).	Integer
Number of previous still births	Number of previous still births	Integer
Number of previous pregnancies with congenital anomalies	Number of previous pregnancies (including non-live births) experience by the mother which resulted in a fetus or child with congenital anomalies.	Integer
Pregnancy medication exposure details		
Exposure to IL-17, IL-23, IL-12/23 inhibotor (medication of interest)		
Drug name(s)	International non-proprietary drug name (i.e. active ingredient(s) of the medicinal product)	a) Bimekizumab b) Brodalumab c) Guselkumab d) Ixekizumab e) Mirikizumab f) Risankizumab g) Secukinumab h) Tildrakizumab i) Ustekinumab

Drug injection dates	Date at which the medication used during the period 6 months before pregnancy until the end of pregnancy	Date (dd/mm/yyyy)
Drug indication(s)	Specific indication for which the medication was used	a) Axial spondylitis b) Crohn's disease c) Psoriasis d) Psoriatic arthritis e) Ulcerative colitis f) Other
Dose per use	Amount of medication administered per use in mg	integer
Frequency of use	Interval in weeks	integer
Comedication (exposure to medication other than the medication of intersest)		
Comedication	Comedication (exposure to medication other than the medication of intersest)	Options: a) Yes, b) No, c) Unknown
Maternal comedication use per trimester	Period in which comedication was used	a) Pre-pregnancy b) First trimester c) Second trimester Third trimester
Paternal comedication	Comedicaiton used in the three months before conception	a) Yes, b) No, c) Unknown
Comedication type		If yes, a) Antibiotics b) Antidepressants c) Antidiabetics d) Antihypertension medication e) Antimalarials f) Antipsychotics g) Anxiolytics h) Cholesterol lowering medication i) Conventionial systemic DMARDs j) bDMARDs (Biologics/Small molecule inhibotors/JAK inhibitors) k) Levothyroxine l) Opioids
Maternal illness and obstetric complication details		
Maternal medical conditions arising in pregnancy	Any maternal medical condition arising during pregnancy	a) Yes, b) No, c) Unknown If yes, a) Gestational diabetes b) Gestational hypertension c) Intrauterine growth retardation d) Preeclampsia e) Premature rupture of membranes f) Vomiting
Gestational age Maternal medical conditions arising in pregnancy	Gestational age at which condition was diagnosed, in days.	
Maternal death	Death of a woman while pregnant or ≤42 days of the end of the pregnancy (including live/stillbirth delivery, ectopic pregnancy, miscarriage or termination) from any cause related to or aggravated by the pregnancy or its management but not from accidental or incidental causes.	Value 1 - Options: a) Yes, b) No, c) Unknown
Delivery details		
Mode of delivery	The methods by which the fetus was delivered from the mother	Value 1 – Options; a) Spontaneous vaginal delivery (incl. vertex/breach, b) assisted vaginal delivery (incl. forceps/ventouse), c) emergency c-section (post-labour/pre-labour), d) elective c-section, e) unknown.
IMID characteristics		
Disease activity	Disease activity score with corresponding date. Maternal exposure: the year before conception and during pregnancy Paternal exposure: the year before conception	Integer
Pregnancy outcome details		
Pregnancy outcome collection status	Status of pregnancy outcome details reported to the system	Options: a) Outcome known, b) Follow-up pending, Lost-to-follow-up, Missing
Date of end of pregnancy	Date at which the pregnancy completes (for all outcomes). For live births, this will be the date of delivery (infant date of birth).	Date (dd/mm/yyyy)

	For terminations/evacuation of retained products of conception, this will be the date the procedure was performed.	
Gestational age at end of pregnancy	Gestational age in days (post-LMP) at the time the pregnancy ended. Calculated as either the time since the first day of the LMP or from prenatal ultrasound scans If necessary, converted from weeks and days (post-LMP) or weeks and days (based on prenatal ultrasound measurements)	Integer
Induced termination	Induced abortion (either medical or surgical) of a pregnancy for any reason	Value 1 - Options: a) Yes, b) No, c) Unknown If, "Yes", Values 2 (reason for termination) - Options: a) Non- medical reason, b) Medical reason (maternal indication), c) Medical reason (fetal indication), d) Other, e) Unknown If "Other", Value 3 (details): Text
Stillbirth	Death of a fetus prior to the complete expulsion or extraction from its mother, after the 22nd completed week post- LMP (≥154 days) of pregnancy; the death is indicated by the fact that after such separation the fetus does not breathe or show any other evidence of life, such as beating of the heart, pulsation of the umbilical cord or definite movement of voluntary muscles	Options: a) Yes, b) No, c) Unknown
Spontaneous abortion	Death of a fetus prior to the complete expulsion or extraction from its mother, before the 22nd completed week of pregnancy (≤153 days).	Options: a) Yes, b) No, c) Unknown
Live/ stillborn birth outcome details		
Gestational timing of live/stillborn offspring	Whether a live birth or stillbirth was preterm, full term, or post-term infant. The directly reported value may be based on the date of LMP or on assessments from prenatal ultrasound scans. Preterm is <37 weeks (<259 days), full-term is ≥37 to <42 weeks (≥259 and <294 days), and post-term is ≥42 weeks (≥294 days).	Options: a) Pre- term, b) Full term, c) Post-term, d) Unknown
Infant birth weight	Weight of the offspring at delivery (in grams)	Integer
Infant sex	Sex of the offspring at birth	Options: a) Male,b) Female
Infant head circumference	Occipito-frontal circumference (i.e. the widest circumference of the skull from the broadest part of the forehead (above the eyebrow and ears) to the most prominent part of the rear of the head), measured using a non- stretchable flexible tape - to be recorded in cms	Integer (in centimeters)
Small for Gestational Age at delivery	An infant born with a birth weight less than the 10th centile on population-level infant birth weight charts	Options: a) Yes, b) No, c) Unknown
Large for Gestational Age at Delivery	An infant born with a birth weight greater than the 90th centile on population-level infant birth weight charts	Options: a) Yes, b) No, c) Unknown
Live born neonatal/infant outcome details		
Postnatal death of live born infant	Details of the death of a live born infant	Value 1 - Options: a) Yes, b) No, c) Unknown If "Yes", Value 2 (date of death): Date If "Yes", Value 3 (MedDRA/ICD cause of death code): Text If "Yes", Value 4 (Coding system) - Options: a) MedDRA, ICD10, c) Other (detail) – Text Value 5 (record additional details of the complication not covered by the coding system): Text Values 6 (age at death category) - Options: a) Infant death, b) Child death, c) Unknown If "Infant death", Values 7 (neonatal death) - Options: a) Yes, b) No, Unknown
Infection in infant	Infection in the first year of life in the infant	Value 1 - Options: a) Yes, b) No, c) Unknown If "Yes", Value 2 – text to describe infection

Infant follow-up age	Age until when the infants was followed. (If, for example, infections are reported only for the first three months of life, please report these infections and state the infant follow-up age here).	
Malformation details		
Congenital anomaly	Presence of any structural/morphological, functional or biochemical anomaly(ies) in the fetus that occur during intrauterine life and can be identified prenatally, at birth or later in life	Options: a). Yes, b) No, c) Unknown
Details of all congenital anomaly(ies)	Details of the anomaly(ies) present in the exposed fetus	Value 1 (diagnosis: free text in accordance with coded diagnostic term(s)): Text Value 2 (MedDRA/ICD diagnosis code): Text Value 3 (Coding system) - Options: a) MedDRA, b) ICD10, c) Other (detail) – Text Value 4 (age at diagnosis): Text
Infant malformation case classification	Classification of status of a fetus / infant case with an anomaly(ies) based on a hierarchy of observed events	Options: a) Genetic malformation case, b) Major malformation case (non-genetic), c) NOS malformation case (non-genetic), d) Minor malformation case (non-genetic).

Appendix 3| Expected number of cases per biologic and per TIS center/registry.

	Type of IL17/IL23 inhibitor	Number of prospective pregnancies with known outcome														
		Germany (Ulm)	Italy	BELpREG	France (Lyon)	Turkey	Israel	MvM	Germany (Berlin)	France (CRAT)	UKTIS	Swiss	Dublin	PRIDE	BioCAPTURE	**Total**
Maternal exposure during pregnancy (+- before conception)	Bimekizumab (L04AC21)	0	0	0	0	0	0	1	1	1	0	0	0	0	0	**3**
	Brodalumab (L04AC12)	0	0	0	0	0	0	0	1	1	0	0	0	0	0	**2**
	Ixekizumab (L04AC13)	1	3	0	0	0	7	0	8	1	0	1	0	0	0	**21**
	Secukinumab (L04AC10)	5	1	0	0	0	20	0	19	24	1	4	0	0	0	**74**
	Totaal IL-17	**6**	**4**	**0**	**0**	**0**	**27**	**1**	**29**	**27**	**1**	**5**	**0**	**0**	**0**	**100**
	Guselkumab (L04AC16)	2	3	0	0	0	5	0	3	3	0	0	0	0	0	**16**
	Risankizumab (L04AC18)	0	0	0	0	0	22	0	2	1	0	1	0	1	0	**27**
	Tildrakizumab (L04AC17)	1	1	0	0	0	1	0	0	0	0	0	0	0	0	**3**
	Totaal IL-23	**3**	**4**	**0**	**0**	**0**	**28**	**0**	**5**	**4**	**0**	**1**	**0**	**1**	**0**	**46**
	Ustekinumab (L04AC05)	**19**	**9**	**6**	**13**	**0**	**79**	**16**	**169**	**51**	**3**	**6**	**1**	**1**	**0**	**373**
Paternal exposure before/at time of conception	Bimekizumab (L04AC21)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
	Brodalumab (L04AC12)	0	0	1	0	0	0	0	0	0	0	0	0	0	0	**1**
	Ixekizumab (L04AC13)	0	1	2	0	0	0	0	1	1	0	0	0	0	0	**5**
	Secukinumab (L04AC10)	2	0	0	0	0	0	2	3	2	0	0	0	0	0	**9**
	Totaal IL-17	**2**	**1**	**3**	**0**	**0**	**0**	**2**	**4**	**3**	**0**	**0**	**0**	**0**	**0**	**15**
	Guselkumab (L04AC16)	0	0	0	0	0	0	0	2	0	0	0	0	0	0	**2**
	Risankizumab (L04AC18)	0	0	0	0	0	0	0	1	0	0	0	0	0	0	**1**
	Tildrakizumab (L04AC17)	0	0	0	0	0	0	0	0	0	0	0	0	0	0	**0**
	Totaal IL-23	**0**	**0**	**0**	**0**	**0**	**0**	**0**	**3**	**0**	**0**	**0**	**0**	**0**	**0**	3
	Ustekinumab (L04AC05)	**3**	**0**	**1**	**1**	**0**	**0**	**5**	**0**	**1**	**0**	**0**	**0**	**0**	**0**	**11**