# Confidential Information

# PASS Information

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|---|---|
| Title: | Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Ixekizumab |
| Version identifier: | Final 1 |
| Date of last version: | 22 September 2016 |
| EU PAS Register No: | EUPAS15481 |
| Active substance: | Ixekizumab |
| Medicinal product(s): | Ixekizumab: Taltz® |
| Product reference: | EMEA/H/C/003943 |
| Procedure number: | Not applicable |
| Marketing authorisation holder(s): | Eli Lilly and Company |
| Joint PASS: | No |
| Research question and objectives: | The objective of this study is to monitor the uptake of ixekizumab among women of childbearing age (ages 15-45), and to monitor the incidence of maternal and fetal/infant outcomes among pregnant women exposed to ixekizumab. If sufficient number of exposures are identified, an additional objective is to study maternal and fetal/infant outcomes among pregnant women exposed to ixekizumab compared to similar women treated with tumor necrosis factor alpha [(TNF)-α] inhibitor biologics.<br>The primary outcome of this cohort study is major congenital malformations of the infant. Secondary outcomes include the following:<br>• Pregnancy outcomes: Recognized spontaneous abortions, stillbirths, elective terminations, preterm delivery, and small for gestational age infants<br>• Infant outcomes: Minor congenital anomalies (up to 12 months of age) and serious infections of the infant (up to six months of age)<br>• Maternal outcomes: Serious infections during pregnancy and serious peri-partum infections |
| Country(-ies) of study: | United States |
| Author: | PPD MPH<br><br>PPD HealthCore, Inc.<br>PPD<br><br>PPD<br>PPD |

# Marketing Authorisation Holder

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|---|---|
| Marketing authorisation holder (MAH) | Eli Lilly |
| MAH contact person | PPD PhD<br>PPD |

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# 2. List of Abbreviations

| Term | Definition |
|---|---|
| **AE** | Adverse event: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. |
| **AR** | Adverse reaction |
| **CI** | Confidence interval |
| **CPT** | Current Procedural Terminology |
| **EMA** | European Medicines Agency |
| **DALY** | Disability-adjusted life year |
| **ENCePP** | European Network of Centres for Pharmacoepidemiology and Pharmacovigilance |
| **ERB** | Ethical review board |
| **EU** | European Union |
| **FDA** | Food and Drug Administration |
| **GPI** | Generic Product Identifier |
| **HCPCS** | Healthcare Common Procedure Coding System |
| **HIPAA** | Health Insurance Portability and Accountability Act |
| **HIRD** | HealthCore Integrated Research Database |
| **HIRE** | HealthCore Integrated Research Environment |
| **HRQoL** | Health-related quality of life |
| **ICD-9-CM** | International Classification of Diseases, Ninth Revision, Clinical Modification |
| **ICD-10** | International Classification of Diseases, Tenth Revision |
| **IgG** | Immunoglobulin G |
| **IL-17** | Interleukin-17 |
| **IR** | Incidence rate |

| | |
|---|---|
| **IRB** | Institutional Review Board |
| **IRR** | Incidence rate ratio |
| **MACDP** | Metropolitan Atlanta Congenital Defects Program |
| **MAH** | Marketing authorisation holder |
| **MCM** | Major congenital malformation |
| **MedDRA** | Medical Dictionary for Regulatory Activities |
| **MRP** | Medical record plan |
| **NDC** | National Drug Code |
| **PAS** | Post-authorisation studies |
| **PPV** | Positive predictive value |
| **PSUR** | Periodic safety update reports |
| **QALY** | Quality adjusted life years |
| **RMP** | Risk management plan |
| **SAP** | Statistical Analysis Plan |
| **TORCH** | Toxoplasmosis, other, rubella, cytomegalovirus, herpes |
| **TNF-α** | Tumor necrosis factor alpha |
| **US** | United States |
| **WHO** | World Health Organization |

# 3. Responsible Parties

Not applicable.

# 4. Abstract

Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Ixekizumab

Amendment 1, Protocol, Final Version 1, 12 September 2017
PPD HealthCore, Inc.

- **Rationale and background**
  Ixekizumab is an interleukin (IL)-17 antagonist approved for the treatment of moderate to severe plaque psoriasis. Pregnant women were not included in the clinical development program, and women who became pregnant during development discontinued the medication. Therefore, information about the association between exposure during pregnancy and maternal and fetal outcomes is limited.

- **Research question and objectives**
  The objective of this study is to monitor the uptake of ixekizumab among women of childbearing age (ages 15-45), and to monitor the incidence of maternal and fetal/infant outcomes among pregnant women exposed to ixekizumab. If a sufficient number of exposures are identified, an additional objective is to study maternal and fetal/infant outcomes among pregnant women exposed to ixekizumab compared to similar women treated with tumor necrosis factor alpha (TNF-α) inhibitor biologics.
  The primary outcome of this cohort study is major congenital malformations of the infant. Secondary outcomes include the following:
  - Pregnancy outcomes: Recognized spontaneous abortions, stillbirths, elective terminations, preterm delivery, and small for gestational age infants
  - Infant outcomes: Minor congenital anomalies (up to 12 months of age) and serious infections of the infant (up to six months of age)
  - Maternal outcomes: Serious infections during pregnancy and serious peri-partum infections

- **Study design**
  This study will include the following phases:
  - Phase I: We will use administrative claims data to monitor the uptake of ixekizumab in the population to determine the frequency of exposure during pregnancy and outcomes of interest. This will allow for assessment of study feasibility and determination of when comparative analyses should occur.
  - Phase II: We will conduct a claims-based cohort study, and will request supplemental medical record data for all patients. Comparative analyses will evaluate maternal, fetal, and/or infant outcomes associated with exposure to ixekizumab, relative to other TNF-α inhibitor biologic medications used to treat psoriasis. If ixekizumab is approved for other indications during the study period, ixekizumab or TNF-α inhibitor treated women with these indications will also be

included. Exposure, outcome, and covariate data will be identified using a combination of administrative claims and medical record review.

- **Population**
  The study will include women exposed to ixekizumab during or within three months before the start of pregnancy as identified through pharmacy and medical claims in the HealthCore Integrated Research Database (HIRD).

  In Phase II, a comparator group of women exposed during pregnancy to other TNF-α inhibitor biologics used to treat psoriasis (e.g., adalimumab, etanercept, or infliximab) or other approved indications of ixekizumab if they are approved during the study period (where conditions and applicable treatments will be defined in an amendment to the Statistical Analysis Plan (SAP)) will be identified. A sensitivity analysis will include secukinumab, brodalumab, guselkumab, and ustekinumab as an alternative comparator group. These newer monoclonal antibodies for treatment of psoriasis are less well understood and may share class effects with ixekizumab.

  Women from both the ixekizumab and comparator groups will be required to have at least six months of baseline eligibility prior to the start of the exposed pregnancy. An exposed pregnancy is defined as having at least one dispensing of ixekizumab or a comparator TNF-α inhibitor biologic during or within three months prior to the estimated pregnancy window. All available data prior to the start of the pregnancy will be used to assess baseline characteristics.

- **Variables**
  Exposure to ixekizumab or comparator TNF-α inhibitor biologics will be ascertained based on the National Drug Code (NDC) or Generic Product Identifier (GPI) for outpatient pharmacy dispensings and based on Healthcare Common Procedure Coding System (HCPCS) codes for infusions that occur in a health care setting. Outcomes (defined in the study objectives) and covariates, including demographics, clinical characteristics, healthcare utilization, and medication use will be ascertained using administrative claims.

  In Phase II, outcomes and exposure timing will be confirmed by medical record review. Covariates not available in the administrative claims, such as lifestyle factors (e.g., smoking status, body mass index, alcohol use) will also be identified from medical records.

- **Data sources**
  This study will be conducted using the HIRD, a broad, clinically rich, and geographically diverse data spectrum of longitudinal medical and pharmacy claims data from health plan members across the US. Depending on accrual of exposed pregnancies, additional data

sources may be added during Phase I (uptake monitoring).

- **Study size**
  The available number of exposed pregnancies will depend on both uptake of ixekizumab in the US among women of childbearing age, and whether such women become pregnant while exposed. With 415 ixekizumab-treated mother-infant pairs and 415 comparator pairs, the study will achieve 80% power to detect a 2.5-fold difference in the birth prevalence of major malformations. If a sufficient number of exposures have not accrued for an interim analysis by second quarter (Q2) 2021, we will reach out to additional data sources to determine the number of ixekizumab exposed pregnancies that would be identified by expanding to a multi-database approach. Feasibility of continuing the study, either as a single database or a multi-database study, will be considered in consultation with regulatory authorities.

- **Data analysis**
  In Phase I, the number of ixekizumab exposures and outcomes among exposed mother-infant pairs will be provided to monitor uptake.

  In Phase II, we will describe women with an ixekizumab or comparator TNF-α inhibitor biologic exposed pregnancy and their infants with respect to demographic, clinical, treatment, and utilization characteristics. In the main analysis, we will address missing data using multiple imputation. We will then calculate an exposure propensity score, which will be used to balance baseline covariates to facilitate group comparisons. For each outcome, we will describe either the incidence rate or the birth prevalence. The applicable estimate will vary by outcome, however each will be presented with 95% confidence intervals (CI).

  Incidence rate ratios and birth prevalence ratios (as applicable) and their 95% CI will then be calculated comparing ixekizumab exposed pregnancies versus comparator TNF-α inhibitor biologic exposed pregnancies, both unadjusted within the propensity score trimmed population, and adjusted for propensity score decile.

  Sensitivity analyses will include analysis without imputation on the subset of patients for whom complete medical record data are available, use of an alternative exposure definition to capture dispensings that overlapped with the beginning of pregnancy, and restriction of the study population to women with at least 12 months of health plan eligibility prior to the start of pregnancy (as sample size allows). We will also calculate incidence rate ratios and birth prevalence ratios comparing ixekizumab users to other monoclonal antibody users. If estimates for the main and sensitivity analyses do not suggest a difference in effect, we will consider an additional analysis that includes both TNF-α and other monoclonal antibody users as part of the comparator group.

# 5. Amendments and Updates

| Amendment or update number | Date | Section of study protocol | Amendment or update | Reason |
|---|---|---|---|---|
| 1 | 12 September 2017 | 8<br>9.3.2<br>9.5 | The primary outcome of the Phase II cohort study was specified as major congenital malformations only. Minor malformations will be evaluated separately. | Change requested by the US Food and Drug Administration (FDA) |
| 1 | 12 September 2017 | 9.2.1 | Revised wording to clarify the comparator group, which does not include off-label ixekizumab users | Change requested by the FDA |
| 1 | 12 September 2017 | 9.2.1 | Added exclusion of mother-infant pairs with both ixekizumab exposure and comparator anti-TNF-α inhibitor exposure to Phase I (uptake monitoring) | Allows assessment of the size of the population with overlapping exposures |
| 1 | 12 September 2017 | 9.2.1 | Revised text to allow for review of alternative strategies to link mothers and infants in the event that subscriber identification number is unavailable | Change requested by the FDA |
| 1 | 12 September 2017 | 9.2.2 | Revised study period to indicate that main analyses will be conducted using data accrued during the period of time when ixekizumab is marketed (i.e., 2016 and on) if sample size permits. A sensitivity analysis will use all available data back to 2006 | This will protect against bias due to underlying changes in exposures, outcome ascertainment, and covariates over time. |
| 1 | 12 September 2017 | Figure 1 | Revised the uptake monitoring flow diagram so that age restriction follows other entry criteria and updated study outcomes modified per protocol changes described above | Improves assessment of the extent to which modifiable study criteria impact study size |
| 1 | 12 September 2017 | 9.3.2 | Revised medical record review approach to allow review of redacted medical records by a panel of clinicians to confirm outcomes that cannot be readily defined via abstraction | Change requested by the FDA |

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| 1 | 12 September 2017 | 9.3.2<br>9.3.3 | Medications of teratogenic potential will be added based on review by a clinician with expertise in teratology | Change requested by the FDA |
| 1 | 12 September 2017 | 9.5 | Clarified that 415 ixekizumab exposed mother-infant pairs are required per the power calculations presented for the primary endpoint (major congenital malformations) | Accounts for the expectation that some mothers and infants will not link successfully. |
| 1 | 21 September 2017 | All | Revised timeframe for assessment of serious infections of the infant (up to six months of age). | Change requested by the FDA |

Abbreviation: No. = number.

# 6. Milestones

| Milestone | Planned date |
|---|---|
| Start of data collection | October 2017 |
| Interim report of study results | June 2021[a] |
| End of data collection | June 2021[b] |
| Final report of study results | June 2022[c] |

[a] An interim analysis will be performed once one-third of targeted ixekizumab exposures have accrued. If a Yes, updated.

sufficient number of exposures have not accrued for an interim analysis by January 2020, available data will be summarised and reported in the periodic safety update reports (PSUR) according to regulated timelines.

[b] If a sufficient number of exposures have not accrued for an interim analysis, the end of data collection is anticipated to be June 2021. If a sufficient sample size can be obtained for an interim analysis, the study will continue for a maximum of eight years to obtain the targeted sample size. In this scenario, the end of data collection is anticipated to be September 2024.

[c] Registration in the European Union (EU) Post-Authorisation Study (PAS) Register was initiated in September 2016. Registration will be complete before the start of data collection. If a sufficient number of exposures have not accrued for an interim analysis, available data will be summarised and reported in the PSUR according to regulated timelines, per commitments to European regulators. This same information will be submitted to the US FDA no later than June 2022. If sufficient sample size can be obtained for an interim analysis, the study will continue for a maximum of eight years to obtain the targeted sample size. A final study report will be submitted with the PSUR/Risk Management Plan (RMP) and within 12 months of study completion (anticipated June 2025).

# 7. Rationale and Background

Psoriasis is a systemic autoimmune condition affected by genetic and environmental factors (National Institutes for Health Research 2015). Population prevalence of diagnosed psoriasis is approximately 2-3% (Menter et al. 2008; National Institute of Arthritis and Musculoskeletal and Skin Diseases 2013). The hallmark of psoriasis is plaques (patches) of inflamed, red skin covered with silvery scales. Approximately 80-90% of patients have the plaque form of psoriasis, causing itching and pain, most typically involving skin of the scalp, trunk, buttocks, and limbs (Menter et al. 2008). Although some autoimmune diseases have been shown to adversely affect pregnancy outcomes, the relation between psoriasis and these outcomes is not well understood. There is some evidence of increased risk of spontaneous abortion, caesarean delivery, low birth weight, macrosomia, large-for-gestational age, and a composite outcome consisting of both prematurity and low birth weight, however it is inconsistent across studies (Bobotsis et al. 2016; Lima et al. 2012).

Most patients with psoriasis are considered to have mild disease, and first line treatments with topical drugs and phototherapy may provide adequate relief of symptoms (Lonnberg et al. 2014). Biologic agents used to treat moderate to severe psoriasis include tumor necrosis factor alpha (TNF-α) inhibitors (adalimumab, infliximab, and etanercept), a p40 subunit of interleukin (IL)-12 and IL-23 (ustekinumab), and agents targeting IL-17 (ixekizumab, secukinumab, and brodalumab, Canavan et al. 2016). Some of these biologic medications are indicated for conditions other than psoriasis, and varying degrees of information exist on their safety during pregnancy. In a review of treatment in rheumatic diseases, for example, no controlled study was found, however some concerns for adverse reactions (ARs) in pregnant women or infants were raised by case reports (Ostensen et al. 2011). Findings from the British Society for Rheumatology Biologics Register do not yield firm conclusions (Verstappen et al. 2011). In inflammatory bowel disease, it has been recognized that infliximab and adalimumab monoclonal antibodies are actively transported across the placenta, and that levels of increased prostaglandins are associated with preterm labor. Several large observational studies have, however, found infliximab and adalimumab to be safe during pregnancy, with no increase in congenital malformations, abnormal newborn growth and development, or other complications (Huang et al. 2014). Only very minimal amounts of TNF-α inhibitor drugs are transferred via breast milk, and are not a likely source of infant harm (Gisbert et al. 2013).

Ixekizumab, a humanized immunoglobulin G (IgG) subclass 4 monoclonal antibody that neutralizes IL-17A, is intended for systemic treatment of individuals with moderate to severe chronic plaque psoriasis (Farahnik et al., 2016). Approval for other indications may be sought in the future. No adverse effects to pregnant mothers or their infants have been observed to date among the 17 inadvertent exposures to pregnant women identified in clinical trial data. It is recognized, however, that IgG does cross the placenta and is central to fetal immunity, with transport increasing as the pregnancy progresses (Kane et al. 2009). Given this and common disease onset prior to age 35 years, when many women will become pregnant, characterization of risks to pregnant mothers and their infants is sought.

# 8. Research Question and Objectives

The objective of this study is to monitor the uptake of ixekizumab among women of childbearing age (ages 15-45), and to monitor the incidence of maternal and fetal/infant outcomes among pregnant women exposed to ixekizumab. If sufficient exposures are identified, an additional objective is to study maternal and fetal/infant outcomes among pregnant women exposed to ixekizumab compared to similar women treated with TNF-α inhibitor biologics.

The primary outcome of the cohort study is major congenital malformations of the infant. Secondary outcomes include the following:

- Pregnancy outcomes: Recognized spontaneous abortions, stillbirths, elective terminations, preterm delivery, and small for gestational age infants.
- Infant outcomes: Minor congenital anomalies (up to 12 months of age) and serious infections of the infant (up to six months of age).
- Maternal outcomes: Serious infections during pregnancy and serious peri-partum infections.

# 9. Research Methods

## 9.1. Study design

This administrative claims based cohort study of ixekizumab exposure during pregnancy will include two phases.

Phase I: Uptake monitoring

- Monitor uptake of ixekizumab in the HIRD and identify outcomes among exposed pregnant women (recognized spontaneous abortions, stillbirths, elective terminations, preterm delivery, small for gestational age infants, serious infections during pregnancy, and serious peri-partum infections) and their infants (major congenital malformations, minor congenital anomalies (up to 12 months of age) and serious infections of the infant (up to six months of age)). Numbers and percentages of patients and outcomes will be presented.
- Results from Phase I uptake monitoring will be used to determine feasibility and optimal timing for initiation of cohort surveillance (Phase II). Uptake monitoring is expected to last until 2021, and may suggest the need to incorporate additional data sources or, in the event of very low use during pregnancy, futility of plans for Phase II (see Section 9.5: Study Size).

Phase II: Cohort surveillance

- Conduct a cohort study with comparative analyses to evaluate maternal and fetal/ infant outcomes associated with exposure to ixekizumab.
- Administrative data will be supplemented with medical record review to confirm the timing of pregnancy, outcomes, and available covariates not captured in claims. We will request supplemental medical record data for all patients.
- Women with pregnancy exposure (see Section 9.2.2: Study period) to ixekizumab will be compared to women with pregnancy exposure to other TNF-α inhibitor biologics used in treatment of psoriasis (e.g., adalimumab, etanercept, or infliximab). If ixekizumab is approved for other indications during the study period, ixekizumab or TNF-α inhibitor exposed pregnant women with these indications will also be included. Women from both the ixekizumab and comparator groups will be required to have at least six months of baseline eligibility prior to the start of the exposed pregnancy. Subgroup analyses may be limited to women with at least one diagnosis of psoriasis or another approved indication of ixekizumab during the baseline period. Infants who are linked to an exposed pregnancy will be followed until the earliest of the end of the first year of life or the end of continuous health plan eligibility.
- Maternal and fetal/infant outcomes and covariates of interest will be identified using both administrative claims data and medical record review. Medical record review will be used to verify exposure timing, confirm outcomes, and assess covariates unavailable in administrative claims such as race and lifestyle factors (e.g., smoking, alcohol use, body mass index).

- Unadjusted and propensity score adjusted incidence rates (IR) and incidence rate ratios (IRR), or birth prevalence rates and birth prevalence ratios with applicable 95% confidence intervals (CI) will be presented as appropriate for each individual outcome.

Traditionally, post-market data collection in pregnant women has occurred within the context of post-marketing pregnancy exposure registries; however, these registries often fail to provide clinically meaningful information due to inadequate enrollment. Enrollment challenges can result from insufficient recruitment efforts, lack of incentives for enrollment, and/or limited drug uptake among women who are pregnant or planning to become pregnant (Charlton and deVries 2012). The two-phase, administrative claims-based cohort study presented here was chosen specifically to address enrollment challenges associated with traditional pregnancy exposure registries. During Phase I, the HIRD will be used to monitor the uptake of ixekizumab. This monitoring will occur without reliance on enrollment or primary data collection, and will identify whether the use of ixekizumab during pregnancy is a public health concern. If a sufficient number of exposures accrue to initiate a comparative analysis (see Section 9.5: Study Size), the analysis can be conducted using the administrative claims and medical chart review. This design will optimize the ability to obtain clinically meaningful information on exposure to ixekizumab during pregnancy by monitoring drug uptake and initiating comparative safety analyses independent of enrollment into a traditional registry.

## 9.2. Setting

### *9.2.1. Population*

The study population will be comprised of women who are exposed to ixekizumab, or in Phase II only, a comparator TNF-α inhibitor biologic used to treat psoriasis)at any time during or in the three months prior to the start of pregnancy. If ixekizumab is approved for other indications during the study period, ixekizumab or TNF-α inhibitor exposed pregnant women with these indications will also be included.

In Phase I, we will determine the number of exposed pregnancies and outcomes available for study. Among all ixekizumab exposed individuals in the HIRD, we will identify individuals meeting the following criteria. These criteria, which will subsequently be used for formation of the Phase II cohort, will include the following.

Inclusion criteria:

- At least one study drug exposure
  - Phase I: ixekizumab only
  - Phase II: ixekizumab or comparator TNF-α inhibitor biologic (adalimumab, etanercept, or infliximab) approved for psoriasis or other approved indications for ixekizumab (if ixekizumab receives approval for other indications during the study period)
- Female sex
- Age 15-45 years

- At least one pregnancy with study drug exposure (see Section 9.2.2: Study Period)
- At least one diagnosis of psoriasis or (other approved indications of ixekizumab, for Phase II (if ixekizumab receives approval for other indications during the study period)

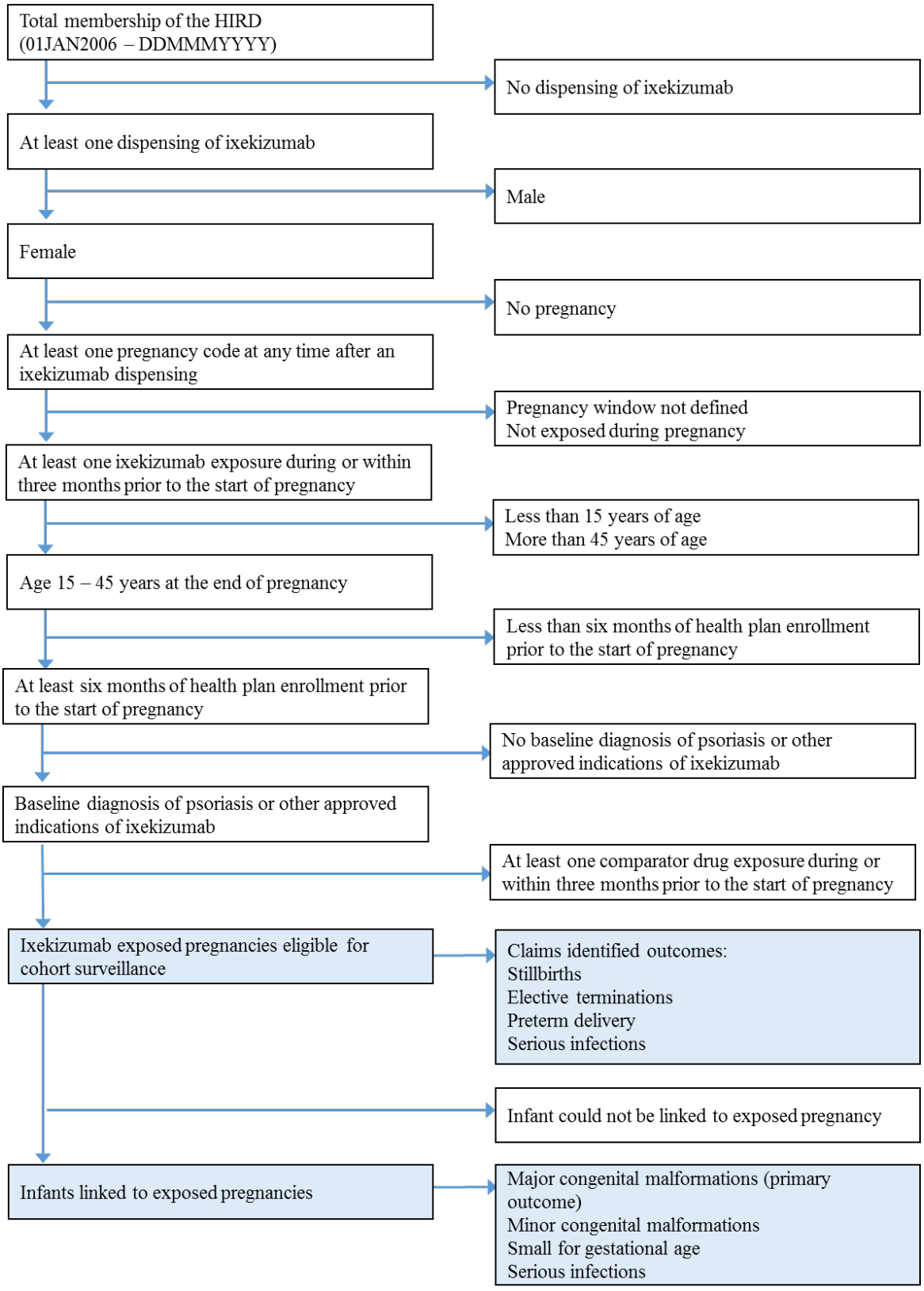
Exclusion criteria:

- Insufficient data to define the start of pregnancy (e.g., diagnosis or procedure indicating pregnancy without a documented outcome, see Section 9.2.2: Study Period)
- Less than six months of continuous health plan eligibility available prior to the start of pregnancy
- Exposure to both ixekizumab and a comparator TNF-α inhibitor biologic during pregnancy
- Phase II only:
    - Mother-infant pairs with exposure to known teratogenic medications (for analysis of congenital malformations only)

For women meeting the inclusion and exclusion criteria defined above, we will also identify linked infants who are captured in the HIRD by requiring that the infant share the mother's subscriber identification number and have a date of birth within 30 days of the recorded delivery date. We will also explore the performance of alternative linking strategies in the event that subscriber identification numbers are unavailable. As shown in Figure 1, the number of patients meeting each criterion will be provided for each attrition step. The numbers for each outcome (see Section 9.3.2: Outcomes) will be provided for the mothers and their linked infants who are eligible for the Phase II cohort.

For the Phase II cohort, all patients meeting these criteria will be included in the main analysis, where we will use multiple imputation to address missing variables not captured due to absent or incomplete medical record data. We will also conduct a sensitivity analysis that will be limited to those mothers and their linked infants for whom at least one medical record was successfully obtained and abstracted to confirm exposures, outcomes, and covariates not otherwise available in claims. The number of patients excluded in this sensitivity analysis due to inability to obtain medical records and their characteristics based on the administrative claims will also be described. Additional details will be provided in the SAP and Medical Record Plan (MRP) that will be finalized at the start of Phase II.

**Figure 1. Ixekizumab uptake monitoring and cohort formation***




*For Phase II, these counts will be provided separately for ixekizumab and comparator TNF-α inhibitor biologics. Dates will be updated at each annual uptake monitoring assessment.

### *9.2.2. Study period*

Data in the HIRD are available retrospectively back to 01 January 2006, but ixekizumab exposures will not accrue until 2016 or later. If a sufficient number of comparator-exposed mother-infant pairs are identified, the study period will start in 2016 for all patients with a sensitivity analysis performed that includes all comparator-exposed pregnancies dating back to 2006. If the number of exposed mother-infant pairs in the comparator group is not sufficient, all available claims data dating back to 2006 will be used as ixekizumab and comparator TNF-α inhibitor biologic exposed pregnancies accrue. It is reasonable to include patients exposed in any calendar year as there is not a strong reason to believe that the relation between the comparator exposure and outcome would be different before and after the launch of ixekizumab. This will maximize the number of pregnancies available for comparison. Calendar year will be included as a covariate so that we may describe the time period when patients are accrued and be transparent about the difference in time periods. The time period limited to the interval when ixekizumab was on the market is preferred as a primary analysis given the possibility of underlying secular trends and changes in technology and healthcare standards through which malformations may be detected and treated.

Because administrative claims data do not specifically identify the date of the last menstrual period (LMP), the following approach to infer the start of pregnancy will be used for screening purposes in Phase I and Phase II.

- Where a gestational age-specific code is recorded at infant delivery, we will subtract the specified number of weeks from the delivery date to establish the start of pregnancy.
- For women with documentation of a full-term delivery without a specified gestational age, we will consider the start of pregnancy to have occurred 42 weeks prior to the date of delivery.
- For women with documentation of a pre-term delivery without a specified gestational age, we will consider the start of pregnancy to have occurred 36 weeks prior to the date of delivery.
- For women with documentation of a spontaneous or elective termination, we will consider the start of pregnancy to have occurred 20 weeks prior to the date of the pregnancy outcome.

A similar approach to identify the start of pregnancy has been applied in past studies for full-term and preterm deliveries (Cole 2007; Mines 2014). Although spontaneous or elective terminations are less described in administrative claims data, we selected this threshold as 20 weeks defines the transition from spontaneous abortion to stillbirth (National Center for Health Statistics 2016).

Where a pregnancy outcome is not observed, the pregnancy window cannot be defined. The number of these possibly exposed pregnancies will be tabulated for descriptive purposes, however they cannot be included in the analysis.

This pregnancy identification approach will overestimate exposure in the initial, claims-based screen to identify candidates for medical record review. After acquisition of medical records, we will use the last menstrual period date captured in the clinical data to redefine the pregnancy window and recalculate timing of exposure.

For women who are exposed during or in the three months prior to the start of pregnancy, the study period will be divided into the pre-pregnancy baseline period (minimum duration of six months), the pregnancy period, and the six-week post pregnancy period to assess baseline covariates, pregnancy exposures, and post-partum events. For infants who are successfully linked to their mother (see Section 9.2.1: Population), follow-up will continue until either the earlier of the end of the infant's continuous health plan eligibility or age 12 months.

Two examples of study period ascertainment are shown in Figure 2.

- Patient A is followed from the start of her continuous health plan eligibility through her full term pregnancy and six weeks post-partum. Her linked infant is then followed until age one year.
- Patient B is followed from the start of her continuous health plan eligibility through her pre-term pregnancy, however her health plan eligibility segment ends at the delivery date/end of the pregnancy period (which could be attributable to either a transfer to a spouse's insurance coverage, job loss, death during delivery, etc.). As such, her six-week post-partum period is not available for analysis, however her pregnancy outcomes would be included in the analyses. Her infant is not identifiable, and is therefore not captured in the cohort for analysis.

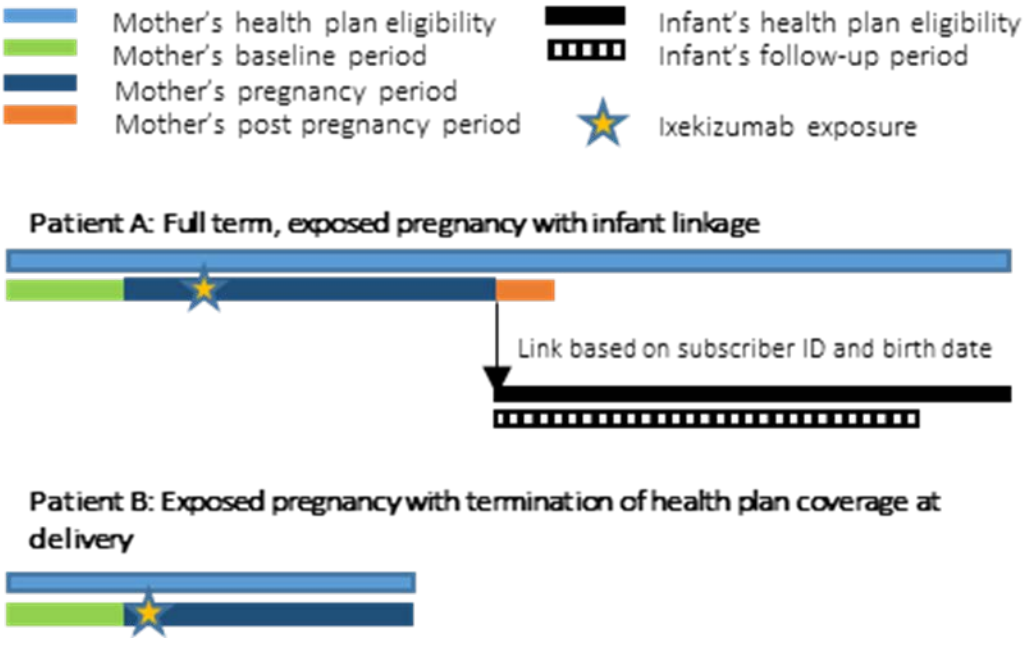



**Figure 2. Observation periods**

## 9.3. Variables

### *9.3.1. Exposures*

Exposure to ixekizumab or comparator TNF-α inhibitor biologics will be ascertained based on the NDC or GPI for outpatient pharmacy dispensings and based on HCPCS codes for infusions that occur in a health care setting. Specific applicable codes will be detailed in a separate SAP.

We will define an exposure as a dispensing or administration of a study drug that occurs either the three months prior to the start of pregnancy or within the pregnancy period (see Section 9.2.2: Study Period), which will be estimated based on the administrative claims in Phase I and confirmed by medical record review in Phase II. A secondary definition of exposure will be defined as a dispensing or administration of a study drug that does not occur within the three months prior to the start of pregnancy but does cross over into the pregnancy period when considering the dispensing date plus the days supplied (for pharmacy dispensings) or exposure time (for infusions). Exposures will be presented overall and stratified by trimester.

Based on the expected biologically relevant exposure window, the time frame for exposure ascertainment may vary for purposes of defining the main analysis for a given outcome. For example, while first trimester exposure may be used as the biologically relevant exposure window for malformation outcomes, exposure later in pregnancy may be more relevant for infection outcomes. We will assess rates for all outcomes during the whole pregnancy and based on exposure by each trimester, and will discuss results in the context of their biologic plausibility. Although any duration of exposure will qualify a patient for inclusion in the study, we will describe the duration of exposure overall, during, or in the three months prior to the start of pregnancy, and during each trimester.

### *9.3.2. Outcomes*

The following study outcomes will be analyzed, with each considered as a separate entity. In Phase I administrative claims data will be used to identify each outcome on the basis of International Classification of Disease, 10th Revision (ICD-10) diagnosis and procedure, Common Procedural Terminology (CPT), and HCPCS codes, which will be detailed in a separate SAP. In Phase II, all outcomes will be confirmed by medical record review for both cohorts, noting that any outcome not captured in the claims data that is identified during medical record review will be counted as a confirmed outcome. Criteria to ascertain each individual malformation will be agreed upon in consultation with clinical experts, and classification will mirror grouping typically used by the Metropolitan Atlanta Congenital Defects Program (MACDP), noting that MACDP codes are not directly available in the HIRD. The same experts will also support development of abstraction forms for identification of covariate and outcome data, and will adjudicate outcomes that are not clearly identifiable from the abstracted data. For these challenging outcomes, two clinicians will independently review medical records that have been redacted of personally identifying information to determine outcome status. Disagreements will be resolved via discussion or review of a third clinician. Full details of the abstraction, redaction and review processes will be included in the MRP.

- Pregnancy outcomes will include the following as identified on medical claims.
    - Outcomes that will be identified based on medical claims from the mother only:
        - Recognized spontaneous abortions
        - Stillbirths
        - Elective terminations
    - Outcomes that will be identified based on medical claims from either the mother or her linked infant within one month of the end of the exposed pregnancy (which allows for capture of data not recorded at the initial hospitalization):
        - Preterm delivery
        - Small for gestational age infants
- Infant outcomes will include the following as identified on either infant medical claims during the first year of life unless otherwise specified (where linked) or maternal claims between the start of pregnancy and the end of the six-week post-partum period. Maternal claims will be used to account for the possibility of infant death prior to establishing a separate member identifier for the infant and occasional mixing of maternal and infant claims in the first few weeks of an infant's life.
    - Major and minor congenital anomalies, both individually and as a composite, including the conditions listed in Annex 4:
        - A composite of all major congenital malformations is the primary endpoint for the cohort study. A table will be provided that shows all defects, defects by class, and within classes where defects are identified, by specific defect.
        - Minor malformations will also be assessed both as a composite and individually.

        - For analysis of major and minor congenital malformations, we will exclude the following infants:
            - Known syndromic or chromosomal cause (e.g., Trisomy 13, Trisomy 18, Trisomy 21, other trisomies and monosomies, Turner's syndrome, other chromosomal anomalies, and other specified congenital malformation syndromes affecting multiple systems).
            - Infants with prenatal exposure to known serious teratogens, including thalidomide and retinoids. Other medications recommended by consulting clinical experts as exclusions or factors to be considered in statistical adjustment will be defined in the SAP.
    - Serious infections of the infant (up to six months of age), defined as a hospitalization with any infection listed as the principal discharge diagnosis or claims for intravenous antibiotics within the first 90 days of life.
        - Hospitalizations with an infection will be classified as follows:
            - By affected body system (e.g., respiratory tract, gastrointestinal tract, urinary tract, etc.).
            - By severity (requiring care in an intensive care unit versus not).
            - By infant age (under versus over two months).
            - Infections related to an injury or burn will not be included in the claims-based outcome definition.
- Maternal outcomes identified from the mother's medical claims:
    - Serious infections during pregnancy, defined as a hospitalization with any infection listed as the principal discharge diagnosis or claims for intravenous antibiotics during the estimated pregnancy window.
        - Hospitalizations with an infection will be classified as follows:
            - By trimester of pregnancy.
            - By affected body system (e.g., respiratory tract, gastrointestinal tract, urinary tract, etc.).
    - Serious peri-partum infections, defined as a hospitalization with any infection listed as the principal discharge diagnosis or claims for intravenous antibiotics within six weeks after the recorded delivery date.
        - Hospitalizations with an infection will be assessed separately for women with a full-term or preterm infant and for those with an incomplete pregnancy.
        - Outcomes will be presented in aggregate and stratified by affected body system.

### *9.3.3. Covariates*

In the Phase I study no additional covariates will be defined. Uptake monitoring will report only counts of exposures, exposed pregnancies, and outcomes as identified in the claims data.

In the Phase II study, the following will be defined for mothers included in the cohort. All will be identified during the pre-pregnancy baseline period unless otherwise specified.

- Demographic and general characteristics:
    - Age (years)
    - US region of residence
    - Duration of health plan eligibility prior to pregnancy
    - Calendar year of pregnancy outcome
- Clinical characteristics will be identified based on ICD-10 diagnosis codes:
    - Autoimmune and inflammatory immune conditions
        - Ankylosing spondylitis
        - Inflammatory bowel disease
            - Crohn's disease
            - Ulcerative colitis
        - Psoriatic arthritis
        - Rheumatoid arthritis
    - TORCH infections during pregnancy
        - Toxoplasmosis
        - Other: syphilis, varicella zoster, parvovirus B19
        - Rubella
        - Cytomegalovirus
        - Herpes
    - Depression
    - Diabetes
    - Hypertension
    - Malignancy
    - 25 most frequently occurring diagnoses recorded (for descriptive analyses)
- Medication use (defined separately prior to and during pregnancy) will be identified based on GPI or HCPCS codes as applicable.
    - Use of medications of known teratogenic potential (note: excludes the mother-infant pair from analysis of major and minor congenital anomalies):
        - Retinoids
        - Thalidomide
        - Others will be added based on consultation with clinical experts
    - Medications used to treat psoriasis:
        - Brodalumab
        - Ixekizumab
        - Secukinumab
        - Apremilast

        - Ustekinumab
        - Adalimumab
        - Infliximab
        - Etanercept
        - Alefacept
        - Cyclosporine
        - Acitretin
        - Methotrexate
        - Guselkumab
    - Medications used to treat other approved indications of ixekizumab:
        - To be defined in an amendment to the SAP if additional indications are approved
    - Medications known to cause immunosuppression:
        - Oral or parenteral steroids
        - Cytostatic agents
        - Drugs acting on immunophilins
        - Interferons
        - Radiation therapy
    - 25 most frequently dispensed medication classes (for descriptive analyses)

Health care utilization (separately within the six months prior to and during pregnancy):

- Count of office visits, emergency department visits, and hospitalizations
- Number of distinct medications used

The following will be defined for linked infants.

- Demographic characteristics:
    - Infant sex
    - US region of residence
    - Duration of health plan eligibility after birth
- Clinical characteristics:
    - 25 most frequently occurring diagnoses recorded
- Medication use:
    - 25 most frequently occurring medication classes used
- Health care utilization:
    - Count of office visits, emergency department visits, and hospitalizations
    - Number of distinct medications used

Additional covariate data will be ascertained based on medical record review.

- Maternal characteristics:
    - Race/ethnicity
    - Relevant family history
    - Relevant obstetric history, including parity and past pregnancy outcomes
    - Body mass index

    - Smoking status
    - Alcohol use
    - Use of prenatal vitamins and supplements
    - Use of over the counter medications
    - Severity of psoriasis
    - Depression
- Infant characteristics:
    - Race/ethnicity
    - Relevant family history
    - Birth weight
    - Gestational age

## 9.4. Data Sources

Initial planned uptake monitoring will occur in the HIRD, a large administrative healthcare database maintained by HealthCore for use in health outcomes and pharmacoepidemiologic research. The HIRD is a broad, clinically rich, and geographically diverse data spectrum of longitudinal medical and pharmacy claims data from commercially-insured health plan members across the US. Member enrollment, medical care (professional and facility claims), outpatient prescription drug use, outpatient laboratory test result data, and health care utilization may be tracked for health plan members in the database dating back to January 2006. As of December 31, 2015, there are 38,829,110 individuals with medical and pharmacy coverage who may be included for research using the HIRD. The HealthCore Integrated Research Environment (HIRE) has the ability to link the claims data in the HIRD to complementary data sources, including inpatient and outpatient medical records, national vital statistics records, cancer and vaccine registries (state-by-state), disease and device registries, individual and provider surveys, point of care clinical data, and clinical oncology data. In past studies involving linkage of mothers and their infants, approximately 70-75% of completed pregnancies could be connected to a qualifying infant. In cases where the infant is not identifiable, it is likely that they were covered by the insurance plan of the other parent.

If uptake monitoring suggests that the number of ixekizumab exposed pregnancies identified in the HIRD is not sufficient, incorporation of additional data sources will be explored. Additional data sources of interest would include a combination of commercially-insured and Medicaid-insured data. If this approach is ultimately required, the Protocol will be amended to describe additional sources as appropriate.

## 9.5. Study Size

The available number of exposed pregnancies will depend on both uptake of ixekizumab in the US among women of childbearing age, and whether such women become pregnant while exposed. It should be noted that specific analyses have additional exclusion criteria in Phase II that are not applied in Phase I (e.g., exclusion of retinoid-exposed pregnancies from the analysis of major congenital malformations), so the counts will provide an approximate study size that may be lower in the final cohort.

With 415 ixekizumab-treated mother-infant pairs and 415 comparator mother-infant pairs, the study will achieve 80% power to detect a 2.5-fold difference in the birth prevalence of major malformations. The effect size that will be detectable with 80% power among a cohort of 415 ixekizumab exposed pairs relative to a cohort of 415 comparator TNF-α inhibitor biologic exposed pairs will vary by outcome as shown below. All calculations assume a two-sided Type I error rate of 0.05 for a two-group Chi-square test of equal proportions.

**Table 1: Minimum detectable risk ratio for study outcomes**

| Outcome | Estimated prevalence | Minimum detectable risk ratio with 415 ixekizumab-exposed subjects and 80% power |
|---|---|---|
| Major malformations | 3% | 2.43 |
| Serious infections of the infant (within six months) | 9% | 1.71 |
| Serious maternal infections within six weeks following delivery | 6% | 1.91 |
| Recognized spontaneous abortions | 20% | 1.42 |
| Stillbirths | 1% | 4.05 |
| Elective terminations | 17% | 1.46 |
| Preterm delivery | 10% | 1.66 |
| Small for gestational age infants | 9% | 1.71 |

An interim analysis and report will be produced after one-third of the targeted ixekizumab exposures for analysis of the birth prevalence of major malformations has accrued. If a sufficient number of exposures have not accrued for an interim analysis by second quarter 2021, we will reach out to additional data sources to determine the number of ixekizumab exposed pregnancies that would be identified by expanding to a multi-database approach, and available data will be summarized and reported. The feasibility of continuing the study either as a single database or a multi-database study will be considered in consultation with regulatory authorities. If an interim analysis is feasible, the study will continue until second quarter 2024 to obtain the targeted sample size. In this case, a final study report will be available second quarter 2025.

## 9.6. Data Management

Datasets and analytic programs will be kept on a secure server and archived per HealthCore record retention procedures. Full details concerning data security and quality assurance procedures will be captured in the SAP. Procedures for acquisition and abstraction of medical record data will be described in a MRP.

## 9.7. Data Analysis

In Phase I, the number of women with prenatal exposure to ixekizumab and maternal and infant outcomes will be provided as specified in Section 9.2.1: Population. No additional analysis is planned.

In Phase II we will describe women with an ixekizumab or comparator TNF-α inhibitor biologic exposed pregnancy by reporting the number and percentage in each cohort for all of the demographic, clinical, treatment and utilization characteristics described in Section 9.3.3: Covariates. We anticipate that missing data will be introduced where medical record confirmation of exposures, outcomes, and covariates is not possible. For example, a facility may refuse to provide the requested record, or the record may not contain a key piece of information required. In the main analysis, we will use a multiple imputation approach in which we will leverage the non-missing data to estimate the true value of missing exposure timing, outcomes, and confounders. This will allow us to retain patients with valuable partial information by using their known covariates to model and assign values of missing variables based on what is observed in patients with non-missing values and similar profiles. We will also conduct a complete case analysis including only those patients with medical record data available, and describe patients who met all inclusion and exclusion criteria for whom at least one medical record could not be obtained. Applicable baseline characteristics (e.g., excluding the 25 most frequently occurring diagnoses and medication used only to describe the cohort) will then be used to calculate an exposure propensity score by modeling the probability of ixekizumab exposure versus a comparator TNF-α inhibitor biologic as a function of the observed covariates. The propensity score will be used to control for confounding. Cohort members whose propensity score is outside the region of overlap will be trimmed and excluded from further analysis.

For each outcome (see Section 9.3.2 Outcomes), we will describe either the IR (calculated as the number of events divided by the person-time at risk) or the birth prevalence (calculated as the number of events divided by the number of births). The applicable estimate will vary by outcome, however each will be presented with 95% CI. Stratified outcome categories will be shown only where there is at least one individual meeting the applicable outcome definition. Incidence rate rations (IRR) and birth prevalence ratios (as applicable) and their 95% CI will then be calculated comparing ixekizumab exposed pregnancies versus comparator TNF-α inhibitor biologic exposed pregnancies. Estimates will be presented unadjusted within the propensity score trimmed population, and adjusted for propensity score decile.

Depending on the frequency of outcomes, rates may be stratified by timing of exposure during pregnancy, and duration of exposure. Planned sensitivity analyses will include:

(1) Use of an alternate exposure definition (see Section 9.3.1: Exposures) to assess the impact of exposures that may have happened very early in pregnancy.
(2) Assessment of an alternative comparator group of monoclonal antibodies; guselkumab, secukinumab, brodalumab, and ustekinumab. These newer medications for treatment of psoriasis or other approved indications of ixekizumab are less well understood and may share class effects with ixekizumab. If estimates for the main and sensitivity analyses do not suggest a difference in effects comparing ixekizumab versus TNF-α inhibitors and ixekizumab versus monoclonal antibodies, we will consider an additional analysis that includes both TNF-α and other monoclonal antibody users as part of a single comparator group to enhance precision.

(3) Restriction of the study population to women with at least 12 months of health plan eligibility prior to the start of pregnancy (as sample size allows).

Additional details of the planned analyses will be described in the SAP.

## 9.8. Quality Control

Full details of the quality control process for data collection, analysis, and reporting are captured in the SAP.

## 9.9. Limitations of the Research Methods

This study integrates a large claims database with medical record review to conduct safety analyses of ixekizumab. To control for confounding by indication, we selected as comparators women being treated with medications approved for the same indications as ixekizumab. Doing so enhances comparability on indication, and on unmeasured factors related to indication that may also be related to outcomes. In addition, medical history and utilization recorded in the claims data may be used to compute propensity scores to further enhance comparability. Despite these efforts, there is potential for residual confounding by covariates not captured in automated claims or medical records.

The main limitations relate to uncertainties regarding the numbers of subjects available to study for a new medication, and limitations inherent in database studies, including accuracy and specificity of codes used to identify outcomes. In particular, the uptake of a new product (plus the follow-up time necessary to observe events) determines the time at which a sufficient study size for analysis will accrue in the database as discussed in Section 9.5: Study Size. Although outcomes and timing of pregnancy will be verified by medical record review, exposure and outcome misclassification may both present issues in the Phase II cohort surveillance study. For example, we will rely on pharmacy dispensing data to determine whether patients used medications, however it is possible that medication was purchased but not used. Likewise, verification of outcomes in the administrative claims will be limited to those outcomes that can be identified in the medical record. For example, a spontaneous abortion early in pregnancy may never come to medical attention, and therefore our outcome is limited to those situations where the patient seeks medical care.

Not all of the outcomes of interest have been validated in administrative claims data, and the performance of ICD-10 codes, which have been used only since October 2015 in the US, has not been well characterized in this setting. As such, we expect that the number of outcomes identified via administrative claims in Phase I uptake monitoring will differ from the number of outcomes verified by medical record review in Phase II cohort surveillance. Although positive predictive value (PPV) and sensitivity of algorithms based on ICD-9 codes have been studied for some outcomes, their performance has been mixed. For example, for major congenital malformations (MCMs), a recent HealthCore study found wide variation in the performance of algorithms. While the PPVs for algorithms that detected specific MCMs were generally very good (PPV>70%), hydrocephalus (47.4%) and several cardiac defects –including atrial septal

defect (37.9%), conotruncal heart defects (68.0%), and pulmonary valve atresia (44.4%)– had lower PPVs.

For some outcomes, high PPV has been reported with mixed findings on sensitivity. For example, ICD-9-CM small for gestational age codes were recently assessed in the US Medicaid Analytic eXtract, and were found to have high PPV (86%) but poor sensitivity (14.2%, Phiri, 2016). Studies from the Danish National Registry of Patients found a PPV of 97.4% (95 CI 92.7-99.5) for spontaneous abortion (Lohse 2010) and 91.1% (95% CI 88.6-93.0) for miscarriage during the second trimester (using ICD-10 codes), however capture of the outcome is limited to those events with medical supervision, and code performance may not generalize to the US. Assessments of stillbirth from administrative datasets in New South Wales, Australia have identified PPVs of 75% (95% CI 59-91) and 89% (95% CI 76-100, Hure 2015). PPV estimates for elective termination were not identified by literature review.

Although use of medical record confirmed cases and verification of pregnancy timing in Phase II present important strengths of the study, it should be recognized that it will not be possible to obtain medical records for all mothers and infants. In cases where a patient seeks care at an out of network provider, for example, the provider is not identifiable in the administrative claims data. In other cases, a facility may not honor the Institutional Review Board (IRB) waiver of Health Insurance Portability and Accountability Act (HIPAA) authorization due to institutional policies and refuse to provide the requested medical record. There may also be cases where a medical record is provided that does not capture the requested history. Although every attempt will be made to obtain the best possible records for mothers and their infants as will be detailed in the MRP, incomplete capture of the cohort may affect generalizability if those for whom medical record data are unavailable or incomplete differ in important ways from those who can be included. Although the proposed use of multiple imputation as well as use of multiple approaches in keeping with European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) guidelines for handling of missing data will help us to better understand the impact of the missing information, differences between individuals with and without missing data will require careful review.

Our proposed approach begins with the composite endpoints, in part because these endpoints will achieve sufficient study size before their components. However, composite endpoints such as major congenital anomalies include many specific endpoints, some of which cannot be identified accurately in claims data, some of which are likely not related to the exposure of interest, and some of which may be associated with the exposure of interest. Because inaccurately coded outcomes, unrelated outcomes, and associated outcomes are grouped together in the composite endpoint, the association between ixekizumab and a composite endpoint may be attenuated compared with the association for a specific endpoint. In other words, the effect of the outcome that is associated with ixekizumab may be partially masked by other conditions that are included in the outcome definition but not associated with ixekizumab use. If a component endpoint is elevated, however, the composite endpoint also will be elevated although to a lesser degree, due to this misclassification.

Elective termination illustrates this misclassification concern. Whereas terminations of interest are those where the termination was motivated by parental knowledge about fetal anomalies, for example, the overall endpoint of elective terminations will comprise these cases and many other more common reasons why a woman may choose to end her pregnancy. If termination due to fetal anomalies was associated with ixekizumab use, but the majority of elective terminations were not due to fetal anomalies and were not associated with ixekizumab use, the overall assessment of the relation between ixekizumab use and elective terminations could easily be null despite a possibly elevated rate ratio for one of the endpoint components. We will explore endpoint components to the best of our ability, however random error will be greater for the specific component endpoints than the composite endpoint, and it may be overwhelming for rare events.

Further, there is some possibility that maternal risk factors identified in the medical record may be more carefully ascertained for infants with outcomes than for infants without outcomes. A diligent clinician may, for example, take a more thorough maternal history for an infant who is very ill than for an infant who is not. Likewise, a complicated or high risk pregnancy will have more clinician encounters and therefore more opportunities for information on lifestyle factors to be collected. We will address this through review of missingness of elements collected from medical record review, which will be captured in such a way that medical records where there was no comment on an item are clearly identifiable (e.g., separating history of smoking: stated that never smoked, versus no data on smoking were identified). The SAP will also include plans for quantitative bias analysis in which any concerning findings regarding differential capture of data will be systematically explored to determine their potential impact on study results.

## 9.10. Other Aspects

Not applicable

# 10. Protection of Human Subjects

Observational studies will be submitted to ethical review boards (ERBs) for approval whenever required by local law. In addition, regardless of local law, all primary data collection observational studies will be submitted to at least one independent body (for example, ERB) per country for review and to confirm that the study is considered non-interventional in that country. Regulatory authorities will be notified and approval sought as required by local laws and regulations. Progress reports will be submitted to ERBs and regulatory authorities as required by local laws and regulations.

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

# 11. Management and Reporting of Adverse Events/Adverse Reactions

**Adverse Events**

During the course of secondary use of data in observational research, information pertaining to ARs for an identifiable patient may be discovered during patient chart review. Researchers will include all protocol defined adverse events (AEs) discovered in the individual patient record/chart associated with ixekizumab in the study datasets. The protocol-defined AEs are specified in Section 9.3: Variables. Researchers will report any other ARs with the attribution explicitly stated in the individual patient records to the appropriate party (for example, regulators or Marketing Authorisation Holder [MAH]) as they would in normal practice as required by applicable laws, regulations, and practices.

# 12. Plans for Disseminating and Communicating Study Results

This study will produce periodic reports that will be delivered to the US FDA and the European Union (EU) European Medicines Agency (EMA).

Results from Phase II may be disseminated via presentation at scientific conferences and/or publication in peer-reviewed journals.

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# Annex 1. List of Standalone Documents

| No. | Document Reference No. | Date | Title |
|---|---|---|---|
| 1. | Not applicable | Not applicable | Statistical Analysis Plan[a] |
| 2. | Not applicable | Not applicable | Medical Record Plan[b] |

[a] This document is planned

[b] This document is planned

# Annex 2. ENCePP Checklist for Study Protocols

**Study title:**

Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Ixekizumab

**Study reference number:**

EMEA/H/C/003943

| **Section 1: Milestones** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 1.1 Does the protocol specify timelines for | | | | |
| 1.1.1 Start of data collection[1] | ☒ | ☐ | ☐ | 6 |
| 1.1.2 End of data collection[2] | ☒ | ☐ | ☐ | 6 |
| 1.1.3 Study progress report(s) | ☐ | ☐ | ☒ | |
| 1.1.4 Interim progress report(s) | ☒ | ☐ | ☐ | 6 |
| 1.1.5 Registration in the EU PAS register | ☒ | ☐ | ☐ | 6 |
| 1.1.6 Final report of study results. | ☒ | ☐ | ☐ | 6 |

Comments:

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

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

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

Comments:

The protocol discusses research questions and study objectives. A full discussion of statistical methods, including formal hypothesis testing as applicable, will be included in the Statistical Analysis Plan.

| Section 3: Study design | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design) | ☒ | ☐ | ☐ | 9.1 |
| 3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection? | ☒ | ☐ | ☐ | 9.1 |

| **Section 3: Study design** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 3.3 Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk) | ☒ | ☐ | ☐ | 9.1 & 9.7 |
| 3.4 Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year) | ☒ | ☐ | ☐ | 9.1 & 9.7 |
| 3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection) | ☒ | ☐ | ☐ | 11 |

Comments:

| |
|---|
| |

| **Section 4: Source and study populations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 4.1 Is the source population described? | ☒ | ☐ | ☐ | 9.4 |
| 4.2 Is the planned study population defined in terms of: | ☒ | ☐ | ☐ | 9.2.2 |
| 4.2.1 Study time period? | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2.2 Age and sex? | ☒ | ☐ | ☐ | 9.4 |
| 4.2.3 Country of origin? | ☒ | ☐ | ☐ | 9.2.1 |
| 4.2.4 Disease/indication? | ☒ | ☐ | ☐ | 9.2.2 |
| 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) | ☒ | ☐ | ☐ | 9.2.1 |

Comments:

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| **Section 5: Exposure definition and measurement** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study) | ☒ | ☐ | ☐ | 9.9 |
| 5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use) | ☒ | ☐ | ☐ | 9.3.1 |
| 5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug? | ☒ | ☐ | ☐ | 9.3.1 |

Comments:

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| **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? | ☐ | ☐ | ☒ | |
| 6.2 Does the protocol describe how the outcomes are defined and measured? | ☒ | ☐ | ☐ | 9.3.2 |
| 6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study) | ☒ | ☐ | ☐ | 9.9 |
| 6.4 Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYsDALYS, DALYS, health care services utilisation, burden of disease, disease management) | ☐ | ☐ | ☒ | |

Comments:

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| **Section 7: Bias** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 7.1 Does the protocol describe how confounding will be addressed in the study? | ☒ | ☐ | ☐ | 9.7 |
| 7.1.1 Does the protocol address confounding by indication if applicable? | ☒ | ☐ | ☐ | 9.7 |
| 7.2 Does the protocol address: | | | | |
| 7.2.1 Selection biases (e.g. healthy user bias) | ☒ | ☐ | ☐ | 9.2.1 & 9.9 |
| 7.2.2 Information biases (e.g. misclassification of exposure and endpoints, time-related bias) | ☒ | ☐ | ☐ | 9.9 |
| 7.3 Does the protocol address the validity of the study covariates? | ☒ | ☐ | ☐ | 9.1 & 9.9 |

Comments:

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| **Section 8: Effect modification** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect) | ☒ | ☐ | ☐ | 9.7 |

Comments:

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|---|
| Stratified analyses are discussed, which offer an avenue for assessment of effect measure modification. Full details of these analyses will be included in the Statistical Analysis Plan. |

| **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: | | | | |

| **Section 9: Data sources** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics) | ☒ | ☐ | ☐ | 9.3.2 |
| 9.1.3 Covariates? | ☒ | ☐ | ☐ | 9.3.3 |
| 9.2 Does the protocol describe the information available from the data source(s) on: | | | | |
| 9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event) | ☒ | ☐ | ☐ | 9.3.2 |
| 9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle) | ☒ | ☐ | ☐ | 9.3.3 |
| 9.3 Is a coding system described for: | | | | |
| 9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System) | ☒ | ☐ | ☐ | 9.3.1 |
| 9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA)) | ☒ | ☐ | ☐ | 9.3.2 |
| 9.3.3 Covariates? | ☒ | ☐ | ☐ | 9.3.3 |
| 9.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other) | ☐ | ☒ | ☐ | |

Comments:

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|---|
| The algorithm that links mothers and babies will be described in the Statistical Analysis Plan. |

| **Section 10: Analysis plan** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 10.1 Is the choice of statistical techniques described? | ☒ | ☐ | ☐ | 9.7 |
| 10.2 Are descriptive analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.3 Are stratified analyses included? | ☒ | ☐ | ☐ | 9.7 |
| 10.4 Does the plan describe methods for adjusting for confounding? | ☒ | ☐ | ☐ | 9.7 |
| 10.5 Does the plan describe methods for handling missing data? | ☒ | ☐ | ☐ | 9.7 |
| 10.6 Is sample size and/or statistical power estimated? | ☒ | ☐ | ☐ | 9.5 |

Comments:

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| **Section 11: Data management and quality control** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving) | ☒ | ☐ | ☐ | 9.6 |
| 11.2 Are methods of quality assurance described? | ☒ | ☐ | ☐ | |
| 11.3 Is there a system in place for independent review of study results? | ☒ | ☐ | ☐ | 12 |

Comments:

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|---|
| Full details concerning data security and quality assurance procedures will be captured in the statistical analysis plan (Section 15).<br><br>A review of all external reports and scientific disclosures is performed by internal groups that are independent of the study teams. |

| **Section 12: Limitations** | **Yes** | **No** | **N/A** | **Section Number** |
|---|---|---|---|---|
| 12.1 Does the protocol discuss the impact on the study results of: | | | | |
| 12.1.1 Selection biases? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.2 Information biases? | ☒ | ☐ | ☐ | 9.9 |
| 12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods) | ☒ | ☐ | ☐ | 9.1 & 9.9 |
| 12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment) | ☒ | ☐ | ☐ | 9.9 |

Comments:

Although the current protocol discusses management of missing data and use of multiple approaches analyse and explore bias from missing data, additional discussion of bias analysis will be included in the Statistical Analysis Plan.

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

Comments:

Full details of data protection requirements will be described in a separate Statistical Analysis Plan.

| Section 14: Amendments and deviations | Yes | No | N/A | Section Number |
|---|---|---|---|---|
| 14.1 Does the protocol include a section to document future amendments and deviations? | ☒ | ☐ | ☐ | 5 |

Comments:

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| |

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

Comments:

| |
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Name of the main author of the protocol: _____

Date: / /

Signature: _____

# Annex 3. Additional Information

PPD

PPD

[redacted]

# Annex 4. Congenital Malformations

- Congenital malformations of the nervous system
  - Anencephaly and similar malformations
  - Encephalocele
  - Microcephaly
  - Congenital hydrocephalus
  - Spina bifida
  - Other congenital malformations of spinal cord, brain or nervous system
- Congenital malformations of eye, ear, face and neck
  - Congenital malformations of eyelid, lacrimal apparatus and orbit
  - Anophthalmos, microphthalmos and macrophthalmos
  - Congenital malformations of eye
  - Congenital malformations of ear
  - Congenital malformations of face and neck (excluding oral cleft)
- Congenital malformations of the circulatory system
  - Congenital malformations of cardiac chambers and connections
  - Congenital malformations of cardiac septa
  - Congenital malformations of pulmonary and tricuspid valves
  - Congenital malformations of aortic and mitral valves
  - Other congenital malformations of heart
  - Congenital malformations of great arteries
  - Congenital malformations of great veins
  - Other congenital malformations of peripheral vascular system
  - Other congenital malformations of circulatory system
- Congenital malformations of the respiratory system
- Cleft lip and cleft palate
- Other congenital malformations of the digestive system
  - Congenital absence, atresia and stenosis of small or large intestine
  - Other congenital malformations of digestive system
- Congenital malformations of genital organs
  - Hypospadias
  - Other congenital malformations of genital organs
- Congenital malformations of the urinary system
  - Renal agenesis and other reduction defects of kidney
  - Cystic kidney disease
  - Congenital obstructive defects of renal pelvis and congenital malformations of ureter
  - Other congenital malformations of kidney or urinary system
- Congenital malformations and deformations of the musculoskeletal system
  - Congenital deformities of hip
  - Congenital deformities of feet

- Polydactyly/Syndactyly
- Reduction defects
- Other congenital musculoskeletal deformities
    - Other congenital malformations of limb(s)
    - Other congenital malformations of skull and face bones
    - Congenital malformations of spine and bony thorax
    - Osteochondrodysplasia with defects of growth of tubular bones and spine
    - Other osteochondrodysplasias
    - Congenital malformations of musculoskeletal system, not elsewhere classified

- Other congenital malformations
    - Congenital ichthyosis
    - Epidermolysis bullosa
    - Other congenital malformations of skin
    - Congenital malformations of breast
    - Other congenital malformations of integument
    - Phakomatoses, not elsewhere classified
    - Congenital malformation syndromes due to known exogenous causes, not elsewhere classified
    - Other congenital malformations, not elsewhere classified

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