NON-INTERVENTIONAL/LOW-INTERVENTIONAL STUDY TYPE 1 STUDY REPORT ABSTRACT

Title: Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project

Date: 07 March 2024

Name and affiliation of the main author: Christina Chambers, University of California San Diego (UCSD) and the Organization of Teratology Information Specialists (OTIS)

Keywords: tofacitinib, Xeljanz, pregnancy, registry

Rationale and background: The goal of this secondary data collection study was to assess the potential impact of tofacitinib exposure during pregnancy on pregnancy and birth outcomes using data from the OTIS pregnancy registry.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the U.S. Food and Drug Administration (FDA), and a category 3 study in the EU RMP.

Research question and objectives: What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes?

The objectives of the study were to monitor pregnancies exposed to tofacitinib and evaluate the risk of tofacitinib relative to the primary outcome of major structural birth defects and the secondary outcomes of spontaneous abortion, stillbirth, preterm delivery, pattern of minor structural birth defects, small for gestational age at birth, and small for postnatal growth, serious or opportunistic infections or malignancies in liveborn children up to 1 year of age.

Study design: This was a prospective cohort study of outcomes in pregnancies exposed to tofacitinib (tofacitinib exposed cohort) compared to outcomes in pregnancies with the same indicated autoimmune disease but unexposed to tofacitinib (disease-matched unexposed cohort), and outcomes in pregnancies without an autoimmune disease and unexposed to tofacitinib (non-diseased unexposed cohort). Pregnancies exposed to tofacitinib that did not meet the cohort eligibility criteria were enrolled in an exposure series (tofacitinib exposure series) as information on their birth outcomes can be useful for hypothesis generating when reviewing the cohort data.

Setting: The study was conducted by the Organization of Teratology Information Specialists.

Subjects and study size, including dropouts: Pregnant women in the U.S. and Canada were enrolled with a targeted sample size of 100 participants per cohort group.

Variables and data sources: Tofacitinib exposure in the cohort was defined as any dose of tofacitinib in the first trimester with or without continued use in pregnancy.

The primary outcome of interest was major structural birth defects. Secondary outcomes of interest were minor structural birth defects, spontaneous abortion, stillbirth, preterm delivery, small for gestational age at birth, and small for age postnatal growth, serious or opportunistic infections and malignancies in liveborn infants up to 1 year of age. Data on exposures, outcomes, and covariates were obtained by maternal interview, medical records and a dysmorphology examination.

Results: This final report is a composite of the cumulative data for women eligible for and enrolled in the study between 14 November 2013 through 30 June 2022.

A total of 211 participants were enrolled into the cohort study between 14 November 2013 and 30 June 2022. Eleven were enrolled in the tofacitinib-exposed cohort, 100 in the disease-matched cohort, and 100 in the non-diseased cohort. An additional 24 participants were enrolled in the tofacitinib exposure series (pregnant women with tofacitinib exposure but who did not meet the cohort study eligibility criteria). Given the limited sample size of the tofacitinib exposed cohort, the following analysis was descriptive only and no comparative analyses controlling for confounding were conducted.

Among the 11 tofacitinib-exposed pregnancies enrolled in the cohort, there was 1 major structural birth defect among 7 pregnancies ending in at least one live born infant (relative to 3/88 in the disease-matched unexposed cohort and 8/92 in the non-diseased matched unexposed cohort), 1 of 9 pregnancies resulting in a spontaneous abortion (relative to 7/97 in the diseased-matched unexposed cohort and 1/97 in the non-diseased unexposed cohort), and 2 of 9 pregnancies resulting in preterm deliveries (relative to 7/87 in the diseased-matched unexposed cohort and 4/93 in the non-diseased unexposed cohort). By definition, based on general population data, approximately 10% of infants are expected to meet the criteria for small for gestational age (SGA) at delivery due to the normal distribution of infant size. In the tofacitinib-exposed cohort, there were 2 infants small for SGA on weight, 1 on head circumference, and 1 small for age on postnatal weight (percentages in the comparator cohorts were at or below the 10^{th} centile for all three measures of SGA). There were no stillbirths (and none in the comparator cohorts), no serious or opportunistic infections (relative to 7/90 in the diseased-matched unexposed cohort and 4/93 in the non-diseased unexposed cohort) or malignancies reported (and none in the comparator cohorts). In the 3 infants who received the dysmorphology examination, no pattern of minor structural birth defects was identified.

Discussion: The rates of specific adverse pregnancy outcomes in this study were based on extremely small numbers of events, and cannot be generalized to the population of tofacitinib-exposed pregnancies. However, there was no evidence of a pattern of major structural birth defects or minor structural birth defects among the tofacitinib-exposed cohort in this study. There were also no stillbirths, and among liveborn infants, there were no serious or opportunistic infections, or malignancies reported in the tofacitinib-exposed cohort in the first year of life.

Additional data provided in the tofacitinib exposure series identified 1 major structural birth defect that was not similar to the one case reported in the tofacitinib-exposed cohort. In the 4 infants in the tofacitinib exposure series who received the dysmorphology examination, no pattern of minor structural defects was identified.

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NON-INTERVENTIONAL (NI)/LOW-INTERVENTIONAL STUDY TYPE 1 (LIS1) FINAL STUDY REPORT

PASS Information

Title	Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project
Protocol number	A3921203
Version identifier of the final study report	1.0
Date	07 March 2024
EU Post Authorization Study (PAS) register number	ENCEPP/SDPP/5703
Active substance	WHO ATC Code: L04AA29 Tofacitinib
Medicinal product	Xeljanz
Product reference	EU/1/17/1178/001-015
Procedure number	EMEA/H/C/004214
Marketing Authorization Holder (MAH)	Pfizer Limited
Joint PASS	No
Research question and objectives	What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes? Objectives 1. To monitor planned and unplanned pregnancies exposed to tofacitinib. 2. To evaluate the possible teratogenic effect of this medication on the primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the

	secondary pregnancy outcomes of spontaneous abortion, stillbirth, preterm delivery, small for gestational age, small for age for postnatal growth of live born children to one year of age. 3. To estimate the incidence of serious or opportunistic infections or malignancies in live born children up to one year of age. 4. To detect any increase in the prevalence or pattern of the above-mentioned outcomes among exposed pregnancies as compared with an internally generated primary comparison group of disease-matched pregnancies, and a secondary comparison group of non-diseased pregnancies, as well as compared to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program. 5. To describe pregnancy outcomes of all tofacitinib-exposed pregnancies enrolled in the exposure series (those not eligible for the cohort).
Country of study	United States and Canada
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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AS	Ankylosing spondylitis
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
DMARD	Disease-modifying anti-rheumatic drug
EDD	Estimated Date of Delivery
EU	European Union
FDA	Food and Drug Administration
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
JIA	Juvenile idiopathic arthritis
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta Congenital Defects Program
MRHD	Maximum Recommended Human Dose
NCHS	National Center for Health Statistics
OTIS	Organization of Teratology Information Specialists
BPRER	Periodic Benefit-Risk Evaluation Report
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
PsA	Psoriatic Arthritis

Abbreviation	Definition
RA	Rheumatoid Arthritis
RMP	Risk management plan
SAE	Serious Adverse Event
SD	Standard deviation
UC	Ulcerative Colitis
US	United States

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
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Nana Koram, PhD, MPH	Epidemiologist	Pfizer. Inc.

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Anthony Scialli, MD Reproductive Toxicology Center	Chair of the Scientific Advisory Board Maternal Fetal Medicine, Developmental Toxicology Specialist
Cheryl Broussard, PhD US Centers for Disease Control and Prevention	Board member Epidemiologist
Megan Clowse, MD Duke University	Board member Rheumatologist
John Graham, MD Cedars Sinai Medical Center	Board member Geneticist
Uma Mahadevan, MD University of California San Francisco	Board Member Gastroenterologist

5. MILESTONES

Milestone[1]	Planned date	Actual date	Comments
Date of institutional review board (IRB) approval of protocol	31 August 2013	05 September 2013	
Start of data collection	01 November 2013	14 November 2013[2]	First participant was enrolled on 14 November 2013
End of data collection	30 September 2023	16 December 2023	
Registration in the EU PAS register		30 January 2014	
Final report of study results	30 March 2024	07 March 2024	

[1] Annual study progress reports and mid-year recruitment and malformation table update reports were included within the periodic benefit-risk evaluation report (PBRER) cycle for tofacitinib.

[2] This is the date of enrollment of the first participant for the rheumatoid arthritis indication. Start of data collection for the other approved indications are as follows: May 2019 for both PsA and UC indications, September 2020 for JIA and December 2021 for AS. The study was open for enrollment on 05 November 2013.

6. RATIONALE AND BACKGROUND

Many rheumatic diseases affect women of childbearing age potential and the medications used to treat these diseases may affect conception, pregnancy, and fetal development (Skomsvoll, 2001). Although improvement of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) disease activity spontaneously occurs in a proportion of pregnancies, many women still require maintenance disease-modifying drug (DMARD) therapy for their conditions. There is some suggestion that women with RA have decreased fecundity (probability of conception) and decreased fertility (ability to conceive) (Nelson, 1997). However, there is no strong evidence that suggests an association between RA and adverse fetal outcome (Nelson, 1997). Disease activity seems to improve in many women with RA during pregnancy, however only a minority are reported to be in complete remission during pregnancy (Barrett et al, 1999; de Man et al, 2008). In 80% of women with psoriatic arthritis (PsA), the disease improved during pregnancy (Ostensen, 1992). Children born to mothers with inflammatory arthritis have an increased incidence of preterm birth, small for gestational age, low birth weight, increased perinatal mortality and congenital malformations (Skomsvoll, 1999). A 3.5% birth defect rate was reported in Norwegian women with specified and non-specified inflammatory arthritis including rheumatoid arthritis. However, the actual number of women with rheumatoid arthritis in this population may not be clear (Skomsvoll, 1999). These adverse outcomes may be related to the underlying autoimmune disease or to concomitant rheumatic therapy. The safety of taking many anti-rheumatic drugs during pregnancy is not clear since experience in humans is often anecdotal.

Studies in women with ulcerative colitis (UC) have shown a higher risk of adverse birth outcomes compared with controls, including low birth weight, preterm delivery, and neonatal death (Cornish, 2007, Stephansson, 2011, Mahadevan, 2018). In addition, UC active disease at the time of conception has been associated with a higher risk of disease relapse during pregnancy (de Lima-Karagiannis, 2016, Mahadevan, 2018).

Tofacitinib is an oral janus kinase (JAK) inhibitor and was first approved in the US in November 2012 for adults with moderately to severely active RA who have had an inadequate response to or intolerance to methotrexate or other disease modifying anti-rheumatic drugs (DMARDs). It is now currently approved in the US for adults with moderately to severely active RA, active PsA, or active AS who have had an inadequate response to or intolerance to one or more tumor necrosis factor (TNF) blockers. It is also approved for the treatment of adults with moderate to severely active UC who have had an inadequate response to or intolerance to one or more TNF blockers, as well as approved for the treatment of polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response to or intolerance to one or more TNF blockers. Additionally, tofacitinib is approved for RA, PsA, and UC in Canada, the EU, and other global regions.

Due to the limited data available on exposure to anti-rheumatic/anti-inflammatory therapies during pregnancy, there is a need to evaluate the safety of tofacitinib use during pregnancy. As per the current prescribing information for tofacitinib, animal reproduction studies have provided evidence of fetocidal and teratogenic effects when pregnant rats and rabbits received tofacitinib during the period of organogenesis at exposures multiples of 73-times and 6.3-times the maximum recommended dose of 10 mg twice daily, respectively. The goal of this registry-based pregnancy study was to assess the potential impact of tofacitinib exposure during pregnancy on pregnancy and birth outcomes.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the U.S. Food and Drug Administration (FDA), and a category 3 study in the EU RMP.

7. RESEARCH QUESTION AND OBJECTIVES

What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes?

7.1. Objectives

1. To monitor planned and unplanned pregnancies exposed to tofacitinib.

2. To evaluate the possible teratogenic effect of tofacitinib relative to primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the secondary pregnancy outcomes of spontaneous abortion, stillbirth, preterm delivery, small for gestational age, small for postnatal growth of live born children to one year of age.

3. To estimate the incidence of serious or opportunistic infections or malignancies in live born children up through one year of age.

4. To detect any increase in the prevalence or pattern of the above-mentioned outcomes among exposed pregnancies as compared with an internally generated primary comparison group of disease-matched pregnancies, and a secondary comparison group of non-diseased pregnancies, as well as compared to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program.[10]

5. To describe pregnancy outcomes of all tofacitinib-exposed pregnancies enrolled in the exposure series (Section 9.3.3) (those not meeting inclusion/exclusion criteria (Section 9.3.2) for the tofacitinib-exposed cohort).

8. AMENDMENTS AND UPDATES

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
1	24 June 2019	Substantial	9.2.2	Inclusion of any approved tofacitinib indication in the exposed and disease comparison groups	Tofacitinib has recently received FDA approval for indications of psoriatic arthritis and ulcerative colitis. This is in addition to the previously approved rheumatoid arthritis indication. The protocol has been amended to include

Table 1. Amendments to the Protocol

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment	Reason
					indications as they are approved.
1	24 June 2019	Administrative	6	Amended final study report date from 31 August 2018 to 30 March 2024	Data collection and study report milestones extended to accommodate new indications, and continue data collection for RA indication, given low recruitment to date.
1	24 June 2019	Administrative	Global	Edited protocol to adapt to new Pfizer protocol template	A new CT24 template had been approved since approval of initial protocol

9. RESEARCH METHODS

The research methods described below are based on the final amended protocol (Version 2.0, Amendment 1, 24 June 2019; Appendix 2).

9.1. Study design

This was a prospective, observational cohort study of pregnancy outcomes in women with a disease for which tofacitinib had an approved indication who were exposed to tofacitinib during pregnancy compared to pregnancy outcomes in women with these same indicated diseases who were not exposed to tofacitinib during pregnancy (disease-matched unexposed comparison group), and pregnancy outcomes in women without an autoimmune disease (non-diseased unexposed comparison group). Women with exposure to tofacitinib during pregnancy who did not meet the study eligibility criteria were enrolled into the exposure-series (Section 9.3.3).

9.2. Setting

The cohort study was conducted by the Organization of Teratology Information Specialists (OTIS) which is a network of university and health department-based telephone information centers serving pregnant women and healthcare providers throughout North America (Leen-Mitchell, et al, 2000). These services receive spontaneous telephone inquiries from women and health care providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and health care provider callers free of charge. These services also provide a basis for collaborative research such as this Registry. Thus, individual Teratogen Information Services located throughout the U.S. and Canada served as a source of referrals not only for tofacitinib-exposed

pregnancies but also for similarly-ascertained pregnant women with an approved indicated disease who did not use tofacitinib and similarly ascertained pregnant women without an autoimmune disease who did not use tofacitinib or any known human teratogen. Enrollment in the Registry was voluntary and required informed consent of the pregnant woman. The Registry enrolled pregnant women who were less than 20 weeks' gestation. This was accomplished by encouraging clinicians to refer patients, and following-up with women planning pregnancy who contact an OTIS service or who self-referred, and direct outreach efforts to target women who were less than 20 weeks' gestation. These efforts reduced possible bias based on prior knowledge of a normal ultrasound, and allowed for better estimation of risk of spontaneous abortion.

The study population included pregnant participants with a disease for which tofacitinib has an approved indication with exposure to tofacitinib during pregnancy, and two comparison groups without tofacitinib exposure during pregnancy (one disease-matched unexposed comparison group and one non-diseased unexposed comparison group) residing in the U.S. or Canada.

9.2.1. Analysis Population ("Cohort Analysis")

Although the Registry collected and followed up on pregnancy reports of all types (including retrospective reports, paternal exposure, off-label indications, etc.) involving tofacitinib, the core of the Registry was a prospective cohort study ("cohort analysis") designed to ascertain and follow-up on cohort-eligible (meeting all inclusion and exclusion criteria) exposures to tofacitinib and to compare these to two internally-generated comparison groups and one external comparison group.

- Comparison Group I consisted of pregnant women who had a disease for which tofacitinib had an approved indication but who did not take tofacitinib, including women who could have taken another medication for their disease during pregnancy.

- Comparison Group II consisted of pregnant women who did not have an autoimmune disease or exposure to any known teratogens. This was a secondary comparison group.

Regarding the risk of major structural defects (primary outcome) among tofacitinib users, external comparison was made to the Metropolitan Atlanta Congenital Defects Program (MACDP), which is a population-based birth defects surveillance program in the U.S. with careful follow-up and classification of major structural defects identified up to six years of age (Correa-Villasenor et al, 2003). This particular program is considered appropriate for external comparison given the fact that it is population based and includes a relatively high level of validation of reported defects identified in children up to six years of age.

9.3. Participants

9.3.1. Inclusion Criteria for "Cohort Analysis" Group

The study enrolled women in three cohorts:

1. **Tofacitinib-Exposed Group - Inclusion Criteria.**

   - Currently pregnant women with an exposure to tofacitinib, for the treatment of a disease for which tofacitinib had an approved indication, for any number of days, at any dose, and at any time from the 1st day of the last menstrual period up to and including the 12th week after the first day of the last menstrual period (LMP), and who may or may not have continued use of tofacitinib later in pregnancy. If the date of LMP was unclear, or if a first-trimester ultrasound had been done and the estimated date of conception was more than one week discrepant from the menstrual period calculation, the first-trimester ultrasound-derived date was used to calculate a date for LMP and conception, and

   - Currently pregnant women who agreed to enroll prior to 20 weeks' gestation, and who had not had prenatal diagnosis of any major structural defect prior to enrollment, and

   - Currently pregnant women, who agreed to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

2. **Comparison Group I: Disease-matched Tofacitinib-Unexposed Cohort – Inclusion Criteria.**

   - Currently pregnant women with a diagnosis of a disease for which tofacitinib had an approved indication, by maternal report and validated by medical records, who had not taken tofacitinib any time since first day of last LMP to delivery in the current pregnancy but who may or may not have taken another medication for their disease including an anti-TNF or other biologic in the current pregnancy. To the extent that tofacitinib-exposed women enrolled in the cohort study also had methotrexate exposure, women in the disease-matched unexposed comparison group I with methotrexate exposure were planned to be recruited to frequency match the number with tofacitinib plus methotrexate, and

   - Currently pregnant women who agreed to enroll prior to 20 weeks' gestation, and who had not had prenatal diagnosis of any major structural defect prior to enrollment, and

   - Currently pregnant women, who agreed to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

3. **Comparison Group II: Non-diseased Tofacitinib-Unexposed Cohort - Inclusion Criteria.**

   - Currently pregnant women who had not had exposure to a known human teratogen or biologic agent as confirmed by the OTIS Research Center, and
   - Currently pregnant women who did not have an autoimmune disease,
   - Currently pregnant women who agreed to enroll prior to 20 weeks' gestation, and who had not had prenatal diagnosis of any major structural defect prior to enrollment, and
   - Currently pregnant women, who agreed to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

9.3.2. Exclusion Criteria for "Cohort Analysis" Group

Potential participants meeting any of the following criteria were not included in the analytic component of the study:

1. **Tofacitinib-Exposed Group - Exclusion Criteria.**

   - Currently pregnant women who had an exposure to tofacitinib during pregnancy but also had an exposure to one or more of the following (either known human teratogens or medications of unknown safety used for the same indication as listed below) during the index pregnancy were not qualified as participants for the tofacitinib-exposure group in the cohort study:
     - Chlorambucil;
     - Cyclophosphamide;
     - Mycophenylate mofetil;
     - Adalimumab;
     - Abatacept;
     - Certolizumab pegol;
     - Etanercept;
     - Tocilizumab;
     - Infliximab;
     - Golimumab;
     - Vedolizumab;

- Secukinumab;
- Ustekinumab;
- Ixekizumab;
- Or leflunomide within one year prior to conception unless a documented blood level below the detectable limit prior to enrollment is available;

- Women who had first contact with the project after prenatal diagnosis of any major structural defect;
- Women who had enrolled in the cohort study with a previous pregnancy;
- Women who had used tofacitinib for an indication other than an approved indicated disease.
- Note: Retrospectively reported cases were followed (see subsequent sections), but were not included in the cohort analysis.

2. Comparison Group I – Exclusion Criteria

- Currently pregnant women who had an exposure to the medications listed below that are known or suspected human teratogens:
  - Chlorambucil;
  - Cyclophosphamide;
  - Mycophenylate mofetil;
  - or leflunomide within one year prior to conception unless a documented blood level below the detectable limit prior to enrollment is available;
- Women who had first contact with the project after prenatal diagnosis of any major structural defect;
- Women who had enrolled in the cohort with a previous pregnancy.

3. Comparison Group II – Exclusion Criteria

- Currently pregnant women who had an exposure to a known teratogen in the first trimester after the time of enrollment were disqualified as participants for purposes of the analysis;
- Women who had a diagnosis of an autoimmune disease;
- Women who had first contact with the project after prenatal diagnosis of any major structural defect;

- Women who had enrolled in the cohort study with a previous pregnancy.

9.3.3. Tofacitinib-exposed Pregnancies not Eligible for the Cohort Study ("Exposure Series")

By study design, pregnancies that did not meet the exposed cohort criteria for reasons described in Sections 9.3.1 and 9.3.2 were excluded from the cohort analysis, however, information on their birth outcomes can be useful for hypothesis generating when reviewing the cohort data. For this reason, women who did not meet the exposed cohort criteria were invited to enroll in a separate "exposure series".

With informed consent, data were collected from maternal questionnaires, medical records review and the physical examination using the same protocol as the cohort study to the extent possible.

9.3.4. Modalities of Recruitment

All exposed participants and comparison participants were recruited through spontaneous callers to participating OTIS member services in locations throughout North America and through active recruitment strategies, e.g., direct mailings to health care specialists, obstetric health care providers, pharmacists, web site, and professional meetings. Each OTIS service provided exposure counseling in the routine manner for all exposed and unexposed women who initially made contact with the service with questions regarding a current pregnancy. Subsequently, each OTIS service requested permission to refer to the Research Center at the University of California, San Diego. Potential participants who agreed to be referred contacted the Research Center or were contacted if they preferred. OTIS member services also referred callers to the Research Center whose exposure to tofacitinib did not qualify for the cohort study (e.g., exposure to tofacitinib only after the first trimester, retrospective reports), as these participants may have qualified for the Exposure Series (Section 9.3.3). Health care providers also contacted the Registry and referred; however, in all cases the mother was the individual who provided informed consent for participation and completed the interview-based data collection.

9.4. Variables

This study used secondary data that is routinely collected as part of the OTIS Pregnancy Registry. Table 2 provides a description of variables included in the study.

Table 2. Variables

Variable	Role	Data source(s)	Operational definition
Exposure to tofacitinib	Exposure	Maternal report Medical record	Maternal report of exposure to tofacitinib of at least one dose any time from first day of last menstrual period (LMP) to end of pregnancy. Confirmation of exposure with medical records.

Table 2. Variables

Variable	Role	Data source(s)	Operational definition
Dose of tofacitinib	Exposure	Maternal report Medical record	Dose of tofacitinib in mg per day (maternal report and confirmation with medical records).
Duration of tofacitinib use	Exposure	Maternal report Medical record	Weeks of tofacitinib use in pregnancy (maternal report and confirmation with medical records).
Indication	Exposure	Maternal report Medical record	Indication for use of tofacitinib (maternal report and confirmation with medical records).
Major structural birth defect	Outcome - primary	Maternal report Medical record OTIS investigator review Dysmorphological Evaluation	The Registry adopted the term “major structural defect” (i.e., birth defect) for an abnormality usually referred to as a “congenital abnormality” and defined major structural defect as follows: Any major structural or chromosomal defect defined and classified, using the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects (CDC 2018). The CDC guidelines disqualify as major structural defects: Those findings that were present in infants with outcomes at <36 weeks gestational age or if gestational age was unavailable, weighing <2500 grams, and were attributed to prematurity alone, such as patent ductus arteriosus (PDA), patent foramen ovale (PFO), and inguinal hernias. Infants with only transient or infectious conditions, or biochemical abnormalities, were classified as being without major structural defects unless there was a possibility that the condition reflected an unrecognized major structural defect.

Table 2. Variables

Variable	Role	Data source(s)	Operational definition
Minor structural defect	Outcome - secondary	Maternal report Dysmorphology Evaluation	A defect which occurs infrequently in the population, which had neither cosmetic nor functional significance to the child and was identified using a study-related checklist incorporated into the study dysmorphology examination of live born infants.
Spontaneous abortion	Outcome - secondary	Maternal report Medical record	Non-deliberate embryonic or fetal death that occurred prior to 20.0 weeks' gestation.
Stillbirth	Outcome - secondary	Maternal report Medical record	A non-deliberate fetal death that occurred at or after 20.0 weeks' gestation but prior to delivery.
Preterm delivery	Outcome - secondary	Maternal report Medical record	A spontaneous or induced delivery at <37 gestational weeks (as counted from LMP), reported by the mother and validated through the medical record.
Small for gestational age	Outcome - secondary	Maternal report Medical record	Birth size (weight, length or head circumference) ≤10th percentile for sex and gestational age using National Center for Health Statistics (NCHS) pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants were used for preterm infants (Olsen 2010).
Postnatal growth deficiency	Outcome - secondary	Medical record	Postnatal size (weight, length or head circumference) ≤10th percentile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for preterm infants.
Lost-to-follow-up	Outcome - secondary	Telephone attempts Mail/Email contact attempts Maternal report	An enrolled participant who withdrew or who failed to complete the outcome interview despite a standard number of telephone attempts and attempt to contact by mail as per study procedure manual within one year of the pregnancy estimated due date.

Table 2. Variables

Variable	Role	Data source(s)	Operational definition
Serious or opportunistic infection	Outcome - secondary	Maternal report Medical record	Defined as those in appendices and infections requiring hospitalization, identified in newborn infants up to one year of age.
Malignancy	Outcome - secondary	Maternal report Medical record	Any malignancy reported in an infant up to one year of age.
Age	Confounder	Maternal report	Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Race	Confounder	Maternal report	Maternal/Paternal race (Caucasian/White, Black, Asian/Pacific Islander, Native American, Other).
Ethnicity	Confounder	Maternal report	Maternal/Paternal ethnicity (Hispanic, Non-Hispanic).
Education	Confounder	Maternal report	Maternal Educational Category (years of completed education <12, 12-15, >15).
Socioeconomic Status	Confounder	Maternal report	Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (categories 1-5).
Height	Confounder	Maternal report	Maternal height (cm).
Pre-pregnancy body weight	Confounder	Maternal report Medical record	Maternal pre-pregnancy body weight (kg) (confirmed with medical record).
Pre-pregnancy BMI	Confounder	Maternal report	Maternal pre-pregnancy BMI categorical (<18.5, 18.5-24.9, 25-29.9, >=30).
Number of times pregnant	Confounder	Maternal report Medical record	Number of times ever pregnant categorical (1, 2-3, 4-5, >=6) (confirmed with medical record).

Table 2. Variables

Variable	Role	Data source(s)	Operational definition
Previous live birth or stillbirth deliveries	Confounder	Maternal report Medical record	Number of previous live birth or stillbirth deliveries categorical (0, 1-2, 3-4, >=5) (confirmed with medical record).
Previous pregnancies ending in spontaneous abortion	Confounder	Maternal report Medical record	Number of previous pregnancies ending in spontaneous abortion categorical (0, 1, 2, >=3) (confirmed with medical record).
Previous pregnancies ending in elective termination	Confounder	Maternal report Medical record	Number of previous pregnancies ending in elective termination categorical (0, 1, 2, >=3) (confirmed with medical record).
Gestational age	Confounder	Maternal report Medical record	Weeks of pregnancy at time of enrollment, continuous and categorical (<13, 13-19.9, >=20): gestational age was calculated from the first date of LMP.
Referral source	Confounder	Maternal report	Source options: Sponsor, OTIS service, HCP, Internet, Other.
Geographic area of residence	Confounder	Maternal report	Geographic area of residence at time of enrollment (i.e., US, Canada).
Disease Symptom/Severity measures	Confounder	Maternal report	Disease Symptom/Severity measures (exposed and disease-matched cohorts only).
Prenatal, Multivitamin, or Folic acid	Confounder	Maternal report	Prenatal, Multivitamin or Folic Acid supplement use by gestational timing categorical (began prior to conception, post-conception only, not taken at all).
Alcohol use in pregnancy	Confounder	Maternal report	Yes/No categorical. Dose and frequency are captured.
Tobacco use in pregnancy	Confounder	Maternal report	Yes/No categorical.

Table 2. Variables

Variable	Role	Data source(s)	Operational definition
Prenatal diagnostic tests prior to enrollment	Confounder	Maternal report Medical record	Tests performed prior to enrollment categorical (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis).
Prenatal diagnostic tests anytime during pregnancy	Confounder	Maternal report Medical record	Tests performed anytime in pregnancy categorical (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis).
Maternal pregnancy exposure to a known human teratogen	Confounder	Maternal report Medical record	Maternal pregnancy exposure to known human teratogen (i.e., methotrexate) (confirmed with medical record).
Years since diagnosis of approved indicated disease	Confounder	Maternal report Medical record	Years since diagnosis of approved indicated disease, continuous.

Abbreviations: BMI = body mass index; CDC = Centers for Disease Control and Prevention; cm = centimeters; kg = kilograms; HCP = health care provider; LMP= last menstrual period; MACDP= Metropolitan Atlanta Congenital Defects Program; NCHS = National Center for Health Statistics; OTIS = Organization of Teratology Information Specialists; US = United States

The Statistical Analysis Plan (SAP) provides detail on the definitions of, the identification of, and the controlling for confounders and/or effect modifiers (Annex 1, Appendix 4).

9.5. Data sources and measurement

The OTIS Research Center was responsible for verifying the participant selection criteria, enrolling each participant and securing informed consent, oral and written (when available or applicable), providing all pregnancy (intake/enrollment and interim I and II) and post-partum follow-up interviews and medical record review, scheduling dysmorphological physical examinations, recording and storage of all data, and subsequent data analysis and interpretation.

Table 3 shows timing of cohort enrollment, interviews, examinations, and medical record request and review.

Table 3. Timing of Cohort Enrollment, Interviews, Examinations, Medical Record Request and Review

	<20 weeks gestation	20-22 weeks gestation[1]	32-34 weeks gestation	0-6 weeks after delivery	0-12 months after delivery	1 year after delivery
Referral	√					
Enrollment and Consent	√					
Intake Interview	√					
Interim Interview I		√				
Interim Interview II			√			
Outcome Interview				√		
Dysmorphological Examination					√	
Medical Record Request and Review				√	√	√
Pediatric Medical Record Review and Questionnaire at 1 Year						√

[1]If participant was enrolled and Intake Interview was conducted between 19 and 20 weeks' gestation, only one Interim Interview was conducted during pregnancy at 32-34 weeks' gestation.

9.5.1. Outcome Classification for Structural Defects for Cohort Study

The method for classifying structural defects for purpose of analysis has been previously described by the study investigators and the OTIS Research Group (MMWR, 2008; Chambers et al, 2001) and has been used in previous studies conducted by this group.

9.5.1.1. Criteria for Structural Defects – Counted/Included

- *Time period for identification:* major structural defects identified up to one year of age by the mother, the health care provider, or identified in the dysmorphological examination were included in the primary analysis. Defects identified after that time frame were described and considered separately.

- *Confirmation of defects:* independent confirmation of certain defects was required. For example, a heart murmur thought to represent a ventricular septal defect that was ascertained by the examining dysmorphologist prior to one year of age was included if it was confirmed as a heart defect by cardiac ultrasound. Similarly, if a midline cutaneous marker at L2-L3 was noted in the dysmorphological examination it was be included as occult spinal dysraphism only if confirmed by appropriate imaging studies. In addition, minor structural defects that were reported only by the mother or medical record but not confirmed by the dysmorphological examination were not included as valid minor defects.

- *Body measurements:* only those growth parameters for which actual measurements were available were considered in the analysis. Measurements of head circumference, length, weight, palpebral fissure length, inner canthal distance, ear length, and philtrum length were taken in dysmorphological examinations. These were compared to mean values for infants of the same age and sex (where sex-specific normative data were available). Less than or greater than two standard deviations from the mean was used to define such terms as microcephaly, hypertelorism, etc.

9.5.1.2. Criteria for Structural Defects – Not Counted/Excluded

- *Birthmarks*: isolated birthmarks were not included as defined by the MACDP (CDC, 2018).

- *Variations of normal:* features on the physical examination which occur in greater than 4 percent of the population and have no cosmetic or functional significance for the child, e.g., 2,3 syndactyly of the toes less than one-third of the distance to the tip of the 3rd phalanx, were not included.

- *Deformational defects:* Those deformational defects that do not require casting or surgery were not included.

- *Time period for identification:* structural defects first ascertained after 12 months of age were not included in the analysis, but considered separately in the context of a possible pattern.

- *Defects identified in spontaneous abortions or elective terminations:* Defects identified by prenatal ultrasound or examination of the products of conception following elective termination or spontaneous abortion were not included in the primary analysis due to potential bias involved in non-uniform use of prenatal diagnosis and pathology evaluation for all abortuses; however, these defects were considered in a separate analysis including all defects in the numerator over all pregnancies with known outcome in the denominator, and in the context of pattern.

9.5.2. Outcome Classification for Secondary Endpoints for Cohort Study

9.5.2.1. Definitions for Secondary Endpoints

- *Spontaneous abortion:* spontaneous abortion was defined as non-deliberate fetal death which occurs prior to 20.0 weeks post-LMP.

- *Stillbirth:* stillbirth was defined as non-deliberate fetal death anytime in gestation at or after 20.0 weeks post-LMP.

- *Preterm delivery:* preterm delivery was defined as live birth prior to 37.0 weeks gestation as counted from last menstrual period (or calculated from first-trimester ultrasound-derived due date if last menstrual period was uncertain or more than one week discrepant).

- *Small for gestational age:* small for gestational age was defined as birth size (weight, length or head circumference) less than or equal to the 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants (CDC, 2000; Olsen et al, 2010).

- *Postnatal growth deficiency:* postnatal growth deficiency was defined as postnatal size (weight, length or head circumference) less than or equal to the 10th centile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for preterm infants if the postnatal measurement was obtained at less than one year of chronological age.

- *Postnatal serious or opportunistic infections, hospitalizations, or malignancies:* Through the one-year postnatal follow-up period, pediatric records were requested with specific requests for documentation of serious opportunistic infections, hospitalizations or malignancies. Serious or opportunistic infections are listed in Annex 1, Appendix 4.

9.5.2.2. Definitions of Other Dispositions for Cohort Study

- *Elective termination:* elective termination was defined as deliberate termination of pregnancy at any time in gestation.

- *Lost-to-follow-up:* Participants were considered lost-to-follow-up if they completed the initial intake interview but subsequently failed to complete the outcome interview and medical records release despite repeated attempts after one year of the from the pregnancy estimated due date. Voluntary participant withdrawals were considered separately.

9.6. Bias

The primary limitation of a cohort study utilizing volunteer participants is potential selection bias. Internal validity was addressed by using comparably selected comparison participants. However, women who agreed to enroll in the cohort study may have represented particularly high or low risk pregnancies, limiting external validity (Johnson et al., 2001).

Rates of very early spontaneous abortion cannot be measured in a study that enrolls women after recognition of pregnancy. For this reason, the results of this study are relevant only to late first-trimester and early second-trimester pregnancy loss.

The registry included pregnancies enrolled prior to outcome, but after a prenatal test had been performed, as long as the test did not indicate the presence of a major structural defect. This practice could have potentially biased the results by lowering the overall

estimate of the prevalence of birth defects (Honein et al., 1999). The data analysis addressed this by stratifying participants based on use of prenatal testing prior to enrollment.

The primary analysis of major structural birth defects was restricted to pregnancies ending in at least one live birth. This approach can bias the estimate of the risk for major birth defects by excluding fetal losses (spontaneous abortions, induced abortions, or fetal deaths) that may have involved major birth defects. To help address this, a secondary analysis of the primary endpoint included the number of pregnancies with known outcome in both the numerator and the denominator. However, the presence or absence of a major birth defect in spontaneous abortions or elective terminations may not be known, thereby introducing a misclassification bias.

Misclassification bias due to poor recall is thought to be reduced in prospective study designs. In addition, each participant was interviewed at several predetermined intervals during pregnancy. Misclassification bias with respect to the infant outcomes was minimized in this study design through the use of a specialized physical examination and a standardized evaluation protocol.

9.7. Study Size

Recruitment goals were originally set at 1-20 participants per year in each of the three groups. The sample size for the study was estimated to be 300 participants for all indications and all cohort groups.

9.7.1. Determination of Sample Size

Based on previous experience with the larger OTIS Autoimmune Diseases in Pregnancy Project, it was estimated that participants would be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated spontaneous abortion and stillbirth rate was 10%, the estimated elective termination rate was 10%, and the estimated lost-to-follow-up rate was 5% (based on previous OTIS experience), resulting in approximately 75 live born infants in each group at the end of recruitment. Experience with the OTIS Autoimmune Diseases in Pregnancy Project demonstrated a yield of approximately 80% live born infants from the total proportion enrolled; therefore, the estimated yield of 75% proposed was conservative. The estimated baseline rates of major structural defects, spontaneous abortion, preterm delivery, and small for gestational age (SGA) and the standard deviation for mean birth weight of full-term infants was based on previous OTIS studies and on general population data. With the proposed sample size, at 80% power, alpha of 0.05, two-tailed tests of significance (except as noted for pattern of minor anomalies), and each comparison group independently compared to the exposed group, the following minimum effect sizes were estimated to be detectable:

Table 4. Sample Size and Power for a Specified Effect Size

Endpoint	N in Each Group	Baseline Rate	RR Detectable	Power[1]
Major Structural Defects[2]	75	3%	5.5 (6.1)	80% (84%)
Specific Pattern of 3 or more minor structural defects	75	1%	10.0	71%[3]
Spontaneous Abortion	85	10%	2.7 (3.0)	80% (88%)
Preterm Delivery	75	10% (6%)	2.8 (4.0)	80% (85%)
Small for Gestational Age	75	10% (7%)	2.8 (3.5)	80%

[1]Based on Fishers Exact Test, 2 tailed, alpha 0.05, except for specific pattern of three or more minor anomalies as noted below; normal approximation using Open Epi software.
[2]Primary endpoint.
[3]Based on one-tailed Fishers Exact Test, alpha 0.05; power = 92% if two comparison groups are combined for n = 150.

9.8. Data Transformation

Detailed methodology for any data transformations are documented in the statistical analysis plan (SAP), which is dated, filed and maintained by the sponsor (Annex 1, Appendix 4).

9.9. Statistical Methods

9.9.1. Main Summary Measures

Descriptive data for maternal characteristics were summarized with means and standard deviations for continuous variables and counts and percentages for categorical variables. Outcomes were summarized with counts and percentages and 95% Confidence Intervals (CI) were presented. Outcomes involving time to event (spontaneous abortion and preterm delivery) were described with left truncated rates expressed as percentages and 95% CIs. Missing data were not counted in the percentages.

9.9.2. Main Statistical Methods

Detailed methodology for summary and statistical analyses of data collected in this study is documented in the statistical analysis plan (SAP) (Annex 1, Appendix 4).

The sample size for the study was projected to be 100 participants in each of the three cohort groups. As recruitment into the tofacitinib-exposed cohort was slower than planned, formal statistical analyses were not considered appropriate due to the low number of recruited participants with exposure to tofacitinib. Therefore, the outcomes in each cohort were summarized descriptively. The proportions for each outcome were presented as point

estimates with their 95% CIs. Data from tofacitinib-exposed pregnancies that did not qualify for the cohort but were included in the exposure series (Section 9.3.3) were summarized separately and are presented in Annex 2 Additional Data, Appendix A.2 and A.3.

Primary Outcome

The primary analysis for the cohort study was a description of the point estimates of the birth prevalence of major structural defects and their 95% CIs in each cohort (by underlying maternal disease and overall) among pregnancies ending in at least one live born infant.

In addition, the point estimates of major structural defects and their 95% CIs were also calculated in each cohort among all pregnancies excluding those that were lost-to-follow-up. For reference, the rate of major structural defects from the most recently published MACDP data was also included.

The specific major structural birth defects reported in each cohort are listed in Annex 2, Table 32.

Secondary Outcomes

Live born infants, including multiples, were included in the analysis of a pattern of minor structural defects. For the analysis of a pattern of minor structural defects, the population only included those infants who received the study-related dysmorphological examination. Although specific patterns cannot be defined within twin pairs who have the same 3 minor defects, it was possible that a pattern could have been identified in one member of a twin pair and a different pattern could have been identified involving the second member of a twin pair. The outcome variable thus may have contained likely correlated data for multiples, and the generalized estimating equations (GEE) approach was used (Liang and Zeger, 1986; Diggle et al, 2002). More specifically, the point estimate for the rate for that outcome with its 95% CI was obtained using logit-binomial link and independent working correlation (R package 'geepack').

The analysis of spontaneous abortion (SAB) was complicated by left truncation in the data, i.e., women entered the study at arbitrary times in gestation. Only those women who enrolled between 0 to 20 weeks' gestation (an inclusion criterion) were eligible for the analysis of SAB. Since they were not followed from gestational age zero, survival analysis methods were used to handle left truncation, as well as right-censoring when a participant was lost-to-follow-up prior to 20 weeks' gestation. The left-truncated Fleming-Harrington estimate at 20.0 weeks' gestation was used to estimate the SAB rate with 95% CIs in each of the cohorts (Liang and Zeger, 1986; Diggle et al, 2002). Stillbirths and elective terminations were analyzed in a similar fashion.

Women who enrolled prior to 37.0 weeks of gestation (an inclusion criterion), and delivered a live born singleton (excluding multiple births) were eligible for the analysis of preterm delivery. These data were analyzed using the left-truncated Fleming-Harrington estimate at 37 weeks' gestation to estimate preterm delivery rates in each of the cohorts along with their 95% CIs.

Endpoints relative to small for gestational age (SGA) at birth and small for age postnatal growth at about one year of age on weight, height and head circumference, respectively,

(excluding multiple births) were all binary endpoints. The analysis of each of these outcomes among singleton live births was calculated as the number and percent for the outcome with its 95% CI for each cohort group.

Endpoints relative to serious or opportunistic infections, and malignancies identified between birth and up to one year of age were all binary endpoints. The analysis of each these outcomes was limited to pregnancies ending in at least one live born infant including multiples. The outcome variable thus may have contained likely correlated data for multiples, and the generalized estimating equations (GEE) approach was used (Liang and Zeger, 1986; Diggle et al, 2002). More specifically, the point estimate for the rate for that outcome with its 95% CIs was obtained using logit-binomial link and independent working correlation (R package 'geepack').

9.9.3. Missing Values

Missing values were described in table footnotes. No imputation was performed.

9.9.4. Sensitivity Analyses

Sensitivity analyses examined the primary outcome excluding human teratogens. Although exposure to known human teratogens, except for methotrexate, was exclusionary for the cohorts, exposure to methotrexate was acceptable in the tofacitinib-exposed and the disease-matched comparator cohort to avoid excluding tofacitinib-exposed participants to what might have been a common co-exposure. Thus, a sensitivity analysis excluding those with methotrexate exposure was conducted for the outcome of major birth defects. Another sensitivity analysis described the primary outcome of major birth defects excluding major birth defects thought to be due to chromosomal or genetic etiologies, as these would be unlikely to be due to prenatal medication exposure. A third sensitivity analysis was conducted within each of two strata, according to whether the participant had prenatal diagnostic testing, such as level II ultrasound, amniocentesis or chorionic villus sampling, prior to enrollment in the study or not. The purpose of this was to address potential bias introduced by prior knowledge of normal prenatal diagnostic testing results in advance of enrollment.

9.9.5. Amendments to the Statistical Analysis Plan

None

9.10. Quality Control

Data used in this study were secondary use of data collected as part of the existing OTIS registry, which has established quality control practices. Interview, and examination data were recorded on hard copies of forms, and medical records and medical record abstraction forms were recorded on electronic or hard copies of forms. These records and forms were retained at the Research Center. Data from these forms were extracted and entered into a customized database located at the Research Center. The data were extracted and entered by trained study personnel with extensive experience with this type of information. Entries were periodically reviewed for logical errors, and a random subset of intake and outcome forms are double-checked for data entry accuracy. The method and duration of storage of data was addressed in the informed consent. All records are maintained for a minimum of 10 years following study completion.

For the primary study endpoint of major structural defects, verification of the outcome identified and classification was performed by blinded review by co-investigator, Kenneth Lyons Jones, MD.

9.11. Protection of Human Subjects

Participant Information and Consent

Verbal informed consent was obtained prior to the participant entering the study (before initiation of study protocol-specified procedures) by study personnel; the nature, purpose, and duration of the study was explained to each participant. Each participant was informed that she could withdraw from the study at any time and for any reason. Each participant was given sufficient time to consider the implications of the study before deciding whether to participate. Those who chose to participate verbally agreed to do so. Written informed consent was requested, but not required by the University of California San Diego IRB.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The final protocol, any amendments, and informed consent documentation were reviewed and approved by the IRB at the University of California San Diego.

Ethical Conduct of the Study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and followed generally accepted research practices described in International Society for Pharmacoepidemiology's Guidelines for Good Pharmacoepidemiology Practices (ISPE, 2016 in accordance with the ethical principles of the Declaration of Helsinki (World Medical Association, 2013) and HIPAA (Health Insurance Portability and Accountability Act) (National Institutes of Health, 2002; Andrews et al., 1996).

10. RESULTS

This final report is a composite of the cumulative data for women eligible for and enrolled in the study between 14 November 2013 through 30 June 2022.

10.1. Participants

An overall sample of 211 participants was enrolled in the prospective cohort study. Of these 11 were enrolled in the tofacitinib-exposed cohort 1, 100 in the disease-matched unexposed cohort 2, and 100 in the non-diseased unexposed cohort 3. Characteristics of those enrolled in the prospective cohorts are described in Table 5.

An additional 24 participants, who did not meet the eligibility criteria for the prospective cohort but who had tofacitinib exposure during pregnancy, were enrolled into the tofacitinib exposure series (18 prospective and 6 retrospective) and are described separately in Annex 2 Additional Data, Appendix A.2. and A.3.

Of the 211 participants enrolled in the cohort study, 2 (18.2%) in the tofacitinib-exposed cohort were lost-to-follow-up, 5 (5.0%) in the diseased comparison cohort, and 7 (7.0%) in the non-diseased comparison cohort. Those pregnancies that were lost-to-follow-up were not included in the outcomes analyzed categorically, e.g., major birth defects. However,

they could be included in analyses of the time-to-event outcomes of spontaneous abortion and preterm delivery if there was at least one day of follow-up after enrollment.

10.2. Maternal Characteristics

Table 5 describes the characteristics of the three cohorts. The mean (standard deviation [SD]) maternal age at estimated delivery date for the tofacitinib-exposed cohort was 32.2 (4.8), compared to 32.9 (4.1) in the diseased unexposed cohort, and 33.1 (4.1) in the non-diseased unexposed cohort. Among participants in each of the cohorts, fewer participants in the tofacitinib group were white (72.7%), compared to participants in the diseased unexposed cohort (89.0%), and non-diseased unexposed cohort (79.0%). Similarly, 72.7% in the tofacitinib-exposed cohort were non-Hispanic, compared to 93.0% in the diseased unexposed cohort, and 84.0% in the non-diseased unexposed cohort respectively. In the tofacitinib-exposed cohort, 100.0% resided in the US, while 89.0% and 87.0% resided in the US in the diseased unexposed and non-diseased unexposed cohorts, respectively. More participants numerically in the tofacitinib-exposed cohort were overweight or obese (50.0%) compared to the diseased unexposed and non-diseased unexposed cohorts (38.0%, and 35.0%, respectively). For the tofacitinib-exposed cohort, the most common source of referral for participants was healthcare professional (81.8%), compared to the diseased unexposed and non-diseased unexposed participants who were most commonly self-referred via the internet (53.0% and 63.0%, respectively).

The majority of participants in all cohorts reported having more than 15 years of education; however, the proportion of more highly educated participants was lower in the tofacitinib-exposed group (54.5%) compared to 81.0% in the diseased unexposed group and 84.0% in the non-diseased unexposed group. Household income above $50,000 per year was reported in 63.6% of the tofacitinib-exposed cohort compared to 84.8% and 87.0% of the comparator cohorts, respectively. Hollingshead socioeconomic status classifications that accounted for both maternal and paternal education and occupations were in the middle and higher three categories in all three cohorts; 90.0% in the tofacitinib-exposed, 96.0% diseased unexposed, and 94.0% non-diseased unexposed.

In the tofacitinib-exposed cohort, 27.2% were primigravid (i.e., current pregnancy was their first), compared to 46.0% in the diseased unexposed group, and 23.0% in the non-diseased unexposed cohort. In the tofacitinib-exposed group, 54.5% had at least one previous live birth or stillbirth delivery, compared to 40.0% in the diseased unexposed group, and 61.0% in the non-diseased unexposed cohort. A total of 31.0-36.4% of women in each cohort had one or more previous pregnancies that ended in spontaneous abortion. Across cohorts, the majority had no previous pregnancies that ended in elective termination (90.9% tofacitinib-exposed cohort, 95.0% diseased unexposed cohort, and 91.0% non-diseased unexposed cohort).

One participant (9.1%) in the tofacitinib-exposed cohort had a previous pregnancy that ended in a major congenital malformation, compared to 4.0% in the diseased unexposed group and 6.0% in the non-diseased unexposed comparison group with a previous pregnancy that ended in a major congenital malformation. No participants in the tofacitinib-exposed group reported a previous preterm delivery, compared to 5.0% in each of the comparison groups.

In the tofacitinib-exposed cohort, 54.5% of participants reported planning pregnancy, while approximately 85% reported planning pregnancy in both of the comparison groups. No participants reported in-vitro fertilization in the tofacitinib-exposed cohort compared to 7.0% in the diseased unexposed comparison and 4.0% in the non-diseased unexposed groups.

Tofacitinib-exposed pregnancies tended to enroll earlier in gestation; the mean (SD) gestational age at enrollment in weeks was 9.8 (3.0) in the tofacitinib-exposed cohort, 12.4 (4.4) in the diseased unexposed cohort, and 14.5 (4.2) in the non-diseased unexposed cohort.

Average years (SD) since first diagnosis of RA, PsA, or UC was similar between the tofacitinib-exposed and diseased unexposed cohorts (7.3 (5.5) and 7.0 (5.2), respectively). Scores on the three RA/PsA disease severity measures were on average higher in the tofacitinib-exposed cohort than the diseased unexposed cohort, indicating more severe or disabling disease. For example, at the time of enrollment, the mean score (SD) on the HAQ-Disability Index was 1.0 (0.7) in the tofacitinib-exposed cohort and 0.5 (0.6) in the diseased unexposed cohort. On the pain scale at enrollment, the mean score (SD) was 34.2 (18.8) in the tofacitinib-exposed cohort and 28.6 (30.7) in the diseased unexposed cohort. Mean scores (SD) on the global effect of the disease at enrollment were 41.5 (24.1) in the tofacitinib-exposed cohort and 24.8 (27.2) in the diseased unexposed cohort. Average scores (SD) on the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) at enrollment were similar between the tofacitinib-exposed group (5.5 (1.6)) and the diseased unexposed comparison group (5.7 (1.0)), with lower scores indicating lower quality of life.

With respect to prenatal/multivitamins or vitamins containing folic acid, a lower percentage of participants in the tofacitinib-exposed group (36.4%) began taking supplements prior to pregnancy compared to 77.0% diseased unexposed, and 70.0% non-diseased unexposed participants. This is relevant with respect to the protective effect of folic acid, as well as the potential impact of unplanned pregnancy. A lower percentage of participants in the tofacitinib-exposed cohort reported any alcohol (18.2%), compared to 36.0% in the diseased unexposed comparison, and 45.0% in the non-diseased comparison. Very few participants (<3.0%) reported any tobacco use during pregnancy. The majority of participants had a level I ultrasound prior to enrollment (72.7% tofacitinib-exposed, 76.0% diseased unexposed, and 83.0% non-diseased unexposed). Fewer than 3.0% of participants across all cohorts had a chorionic villi sampling (CVS) or amniocentesis at any time during pregnancy.

Of those in the tofacitinib-exposed cohort, by inclusion criteria, all were exposed at least in the first trimester, and 33.3% were exposed to tofacitinib only in the first trimester. Exposure to systemic corticosteroids was similar between the tofacitinib-exposed cohort and the diseased unexposed group (27.3% and 28.0%, respectively). No participants in the tofacitinib-exposed cohort, and one in the diseased unexposed cohort were exposed to methotrexate during pregnancy.

The only reported comorbidities in the tofacitinib-exposed cohort group were depression (27.3%), and chronic hypertension (9.1%). Depression was also the most common comorbidity but was less frequently reported in the diseased unexposed comparison group (17.0%). Chronic hypertension was reported in only 2.0% of participants in both the diseased unexposed and non-diseased unexposed comparison group

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
Maternal Demographics							
Maternal age (years) at estimated delivery date, categorical, n (%)							
<25 years	0	0	0	0	0	0	2 (2.0)
25-29 years	0	4 (57.1)	4 (36.4)	11 (22.4)	15 (29.4)	26 (26.0)	22 (22.0)
30-34 years	1 (25.0)	2 (28.6)	3 (27.2)	22 (44.9)	15 (29.4)	37 (37.0)	31 (31.0)
>34 years	3 (75.0)	1 (14.3)	4 (36.4)	16 (32.7)	21 (41.2)	37 (37.0)	45 (45.0)
Maternal Age at Estimated Due Date - Mean (Standard Deviation)	36.4 (3.1)	29.8 (3.8)	32.2 (4.8)	33.0 (4.4)	32.8 (3.8)	32.9 (4.1)	33.1 (4.1)
Maternal race, n (%)							
White	2 (50.0)	6 (85.7)	8 (72.7)	40 (81.6)	49 (96.0)	89 (89.0)	79 (79.0)
Black	0	0	0	1 (2.0)	1 (2.0)	2 (2.0)	5 (5.0)
Asian/Pacific Islander	0	0	0	1 (2.0)	1 (2.0)	2 (2.0)	10 (10.0)
Native American	2 (50.0)	0	2 (18.2)	2 (4.1)	0	2 (2.0)	1 (1.0)
Other	0	1 (14.3)	1 (9.1)	5 (10.2)	0	5 (5.0)	5 (5.0)
Maternal ethnicity, n (%)							
Non-Hispanic	4 (100.0)	4 (57.1)	8 (72.7)	43 (87.8)	50 (98.0)	93 (93.0)	84 (84.0)
Hispanic	0	3 (42.9)	3 (27.3)	6 (12.2)	1 (2.0)	7 (7.0)	16 (16.0)
Maternal education category, n (%)							
<12 years	1 (25.0)	0	1 (9.1)	1 (2.0)	0	1 (1.0)	1 (1.0)
12-15 years	2 (50.0)	2 (28.6)	4 (36.4)	9 (18.4)	9 (17.6)	18 (18.0)	15 (15.0)
>15 years	1 (25.0)	5 (71.4)	6 (54.5)	39 (79.6)	42 (82.4)	81 (81.0)	84 (84.0)

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
Hollingshead socioeconomic categor[a], n (%) Low (4 or 5) Medium to High (1, 2, or 3)	 1 (33.3) 2 (66.7)	 0 7 (100.0)	 1 (10.0) 9 (90.0)	 3 (6.1) 46 (93.9)	 1 (2.0) 50 (98.0)	 4 (4.0) 96 (96.0)	 6 (6.0) 94 (94.0)
Maternal Height (cm) - Mean (Standard Deviation)	160.7 (7.0)	170.5 (8.0)	166.9 (8.8)	167.0 (6.9)	166.2 (6.9)	166.6 (6.9)	166.5 (6.2)
Maternal Pre-pregnancy Body Weight (kg) - Mean (Standard Deviation)[b]	64.9 (3.7)	87.3 (28.5)	80.6 (25.8)	76.0 (25.5)	68.9 (17.5)	72.4 (22.0)	67.6 (13.4)
Maternal pre-pregnancy body mass index (BMI)[c], n (%) <18.5 (underweight) 18.5-<25 (normal weight) 25-<30 (overweight) ≥30 (obese)	 0 3 (100.0) 0 0	 0 2 (28.6) 3 (42.9) 2 (28.6)	 0 5 (50.0) 3 (30.0) 2 (20.0)	 2 (4.1) 24 (48.9) 14 (28.6) 9 (18.4)	 3 (5.9) 33 (64.7) 9 (17.6) 6 (11.8)	 5 (5.0) 57 (57.0) 23 (23.0) 15 (15.0)	 2 (2.0) 63 (63.0) 23 (23.0) 12 (12.0)
Gestational Age at Time of Enrollment – Weeks - Mean (Standard Deviation)	9.6 (3.3)	10.0 (3.0)	9.8 (3.0)	12.3 (3.9)	12.4 (4.9)	12.4 (4.4)	14.5 (4.2)
Gestational Age at Time of Enrollment Category – Weeks, n (%) ≤13 weeks >13 - <20 weeks ≥20 weeks	 3 (75.0) 1 (25.0) 0	 6 (85.7) 1 (14.3) 0	 9 (81.8) 2 (18.2) 0	 26 (53.1) 23 (46.9) 0	 28 (54.9) 23 (45.1) 0	 54 (54.0) 46 (46.0) 0	 32 (32.0) 68 (68.0) 0

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
Referral source, n (%)							
Sponsor	0	0	0	0	0	0	0
Health-care Professional	3 (75.0)	6 (85.7)	9 (81.8)	14 (28.6)	11 (21.6)	25 (25.0)	6 (6.0)
Internet	1 (25.0)	0	1 (9.1)	23 (46.9)	30 (58.8)	53 (53.0)	63 (63.0)
OTIS Member Service	0	1 (14.3)	1 (9.1)	3 (6.1)	1 (2.0)	4 (4.0)	16 (16.0)
Other	0	0	0	9 (18.4)	9 (17.6)	18 (18.0)	15 (15.0)
Country of residence, n (%)							
U.S.	4 (100.0)	7 (100.0)	11 (100.0)	45 (91.8)	44 (86.3)	89 (89.0)	87 (87.0)
Canada	0	0	0	4 (8.2)	7 (13.7)	11 (11.0)	13 (13.0)
Family Income Category[d], n (%)							
<$10,000	1 (25.0)	0	1 (9.1)	0	0	0	4 (4.0)
$10,000 – <$50,000	1 (25.0)	2 (28.6)	3 (27.3)	12 (25.0)	3 (5.9)	15 (15.2)	9 (9.0)
≥$50,000	2 (50.0)	5 (71.4)	7 (63.6)	36 (75.0)	48 (94.1)	84 (84.8)	87 (87.0)
Year of Enrollment, n (%)							
Years 2010-2014	1 (25.0)	0	1 (9.1)	19 (38.8)	0	19 (19.0)	12 (12.0)
Years 2015-2018	2 (50.0)	2 (28.6)	4 (36.4)	12 (24.5)	9 (17.6)	21 (21.0)	33 (33.0)
Years 2019-2023	1 (25.0)	5 (71.4)	6 (54.5)	18 (36.7)	42 (82.4)	60 (60.0)	55 (55.0)
Intended Pregnancy, n (%)	1 (25.0)	5 (71.4)	6 (54.5)	38 (77.6)	48 (94.1)	86 (86.0)	83 (83.8)
In Vitro Fertilization (IVF), n (%)	0	0	0	4 (8.2)	3 (5.9)	7 (7.0)	4 (4.0)
Paternal Demographics							

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
Paternal age (years) at estimated delivery date, categorical[e], n (%)							
<25 years	0	1 (14.3)	1 (9.1)	3 (6.5)	1 (2.1)	4 (4.3)	2 (2.1)
25-29 years	0	1 (14.3)	1 (9.1)	6 (13.0)	12 (25.5)	18 (19.4)	20 (20.8)
30-34 years	1 (25.0)	3 (42.9)	4 (36.4)	16 (34.8)	17 (36.2)	33 (35.5)	32 (33.3)
>34 years	3 (75.0)	2 (28.6)	5 (45.5)	21 (45.7)	17 (36.2)	38 (40.9)	42 (43.8)
Paternal Age at Estimated Due Date - Mean (Standard Deviation)	37.5 (2.9)	32.0 (6.5)	34.0 (6.0)	34.8 (6.7)	33.1 (4.4)	34.0 (5.7)	33.9 (5.2)
Pregnancy History							
Gravidity – Number of times ever pregnant, n (%)							
1	0	3 (42.9)	3 (27.2)	22 (44.9)	24 (47.0)	46 (46.0)	23 (23.0)
2-3	1 (25.0)	4 (57.1)	5 (45.5)	15 (30.6)	21 (41.2)	36 (36.0)	62 (62.0)
4-5	2 (50.0)	0	2 (18.2)	10 (20.4)	5 (9.8)	15 (15.0)	9 (9.0)
≥6	1 (25.0)	0	1 (9.1)	2 (4.1)	1 (2.0)	3 (3.0)	6 (6.0)
Parity – Number of previous live birth or stillbirth deliveries, n (%)							
0	2 (50.0)	3 (42.9)	5 (45.5)	26 (53.1)	34 (66.7)	60 (60.0)	39 (39.0)
1-2	1 (25.0)	4 (57.1)	5 (45.5)	15 (30.6)	16 (31.3)	31 (31.0)	54 (54.0)
3-4	0	0	0	7 (14.3)	0	7 (7.0)	5 (5.0)
≥5	1 (25.0)	0	1 (9.0)	1 (2.0)	1 (2.0)	2 (2.0)	2 (2.0)

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
Number of previous pregnancies ending in spontaneous abortion[f], n (%) 0 1 2 ≥3	 1 (25.0) 1 (25.0) 2 (50.0) 0	 6 (85.7) 1 (14.3) 0 0	 7 (63.6) 2 (18.2) 2 (18.2) 0	 33 (67.3) 11 (22.5) 3 (6.1) 2 (4.1)	 36 (70.6) 9 (17.6) 5 (9.8) 1 (2.0)	 69 (69.0) 20 (20.0) 8 (8.0) 3 (3.0)	 65 (65.0) 27 (27.0) 5 (5.0) 3 (3.0)
Number of previous pregnancies ending in elective termination, n (%) 0 1 2 ≥3	 3 (75.0) 1 (25.0) 0 0	 7 (100.0) 0 0 0	 10 (90.9) 1 (9.1) 0 0	 48 (98.0) 1 (2.0) 0 0	 47 (92.2) 4 (7.8) 0 0	 95 (95.0) 5 (5.0) 0 0	 91 (91.0) 7 (7.0) 2 (2.0) 0
Previous pregnancies with a major birth defects, n (%)	0	1 (14.3)	1 (9.1)	2 (4.1)	2 (3.9)	4 (4.0)	6 (6.0)
Previous pregnancies ending in preterm delivery, n (%)	0	0	0	3 (6.1)	2 (3.9)	5 (5.0)	5 (5.0)
Maternal Disease							
Years Since Diagnosis of Primary Disease – Year – Mean (Standard Deviation)	7.3 (3.7)	7.3 (6.6)	7.3 (5.5)	6.5 (5.0)	7.5 (5.4)	7.0 (5.2)	----

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
Maternal Age at Diagnosis of Primary Disease – Years – Mean (Standard Deviation)	28.3 (4.4)	21.7 (7.4)	24.1 (7.1)	25.8 (6.3)	24.4 (5.8)	25.1 (6.0)	----
RA Disease Severity Score							
-Intake - Rheumatic 1[g,j]- Mean (Standard Deviation)	1.0 (0.7)	----	1.0 (0.7)	0.5 (0.6)	0.0 (----)	0.5 (0.6)	----
-Intake - Rheumatic 2[h,k]- Mean (Standard Deviation)	34.2 (18.8)	----	34.2 (18.8)	28.6 (30.7)	0.0 (----)	28.6 (30.7)	----
-Intake - Rheumatic 3[i,l]- Mean (Standard Deviation)	41.5 (24.1)	----	41.5 (24.1)	24.8 (27.2)	0.0 (----)	24.8 (27.2)	----
-2nd Trimester (20 week) - Rheumatic 1[g,j]- Mean (Standard Deviation)	0.5 (----)	----	0.5 (----)	0.5 (0.6)	0.0 (----)	0.5 (0.6)	----
-2nd Trimester (20 week) - Rheumatic 2[h,k]- Mean (Standard Deviation)	35.0 (----)	----	35.0 (----)	21.9 (23.3)	0.0 (----)	21.9 (23.3)	----
-2nd Trimester (20 week) - Rheumatic 3[i,l]- Mean (Standard Deviation)	35.0 (----)	----	35.0 (----)	23.0 (23.3)	0.0 (----)	23.0 (23.3)	----
-3rd Trimester (32 week) - Rheumatic 1[g,j]- Mean (Standard Deviation)	0.8 (----)	----	0.8 (----)	0.4 (0.5)	0.0 (----)	0.4 (0.5)	----
-3rd Trimester (32 week) - Rheumatic 2[h,k] – Mean (Standard Deviation)	30.0 (----)	----	30.0 (----)	20.9 (23.2)	0.0 (----)	20.9 (23.2)	----

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
-3rd Trimester (32 week) - Rheumatic 3[i,l]– Mean (Standard Deviation)	25.0 (----)	----	25.0 (----)	19.0 (22.9)	0.0 (----)	19.0 (22.9)	----
UC Disease Severity Score							
-Intake – UC[m,n] – Mean (Standard Deviation)	----	5.5 (1.6)	5.5 (1.6)	5.1 (----)	5.7 (1.0)	5.7 (1.0)	----
-2nd Trimester (20 week) – UC[m,o] - Mean (Standard Deviation)	----	6.7 (0.3)	6.7 (0.3)	4.5 (----)	6.0 (1.0)	5.9 (1.0)	----
-3rd Trimester (32 week) – UC[m,p] - Mean (Standard Deviation)	----	6.5 (0.4)	6.5 (0.4)	4.0 (----)	6.2 (0.7)	6.2 (0.8)	----
Maternal Exposure							
Prenatal, multivitamin or folic acid supplement use and timing in pregnancy, n (%) Began prior to conception Post conception only Have not taken at all	 0 3 (75.0) 1 (25.0)	 4 (57.1) 3 (42.9) 0	 4 (36.4) 6 (54.5) 1 (9.1)	 37 (75.5) 12 (24.5) 0	 40 (78.4) 10 (19.6) 1 (2.0)	 77 (77.0) 22 (22.0) 1 (1.0)	 70 (70.0) 30 (30.0) 0
Any alcohol use in pregnancy, n (%)	1 (25.0)	1 (14.3)	2 (18.2)	14 (28.6)	22 (43.1)	36 (36.0)	45 (45.0)
Any tobacco use in pregnancy, n (%)	0	0	0	1 (2.0)	1 (2.0)	2 (2.0)	2 (2.0)
Any caffeine use in pregnancy, n (%)	3 (75.0)	5 (71.4)	8 (72.7)	44 (89.8)	48 (94.1)	92 (92.0)	83 (83.0)

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
Prednisone and/or Systemic Oral Corticosteroid Use, n (%)	1 (25.0)	2 (28.6)	3 (27.3)	16 (32.7)	12 (23.5)	28 (28.0)	1 (1.0)
Methotrexate Use in Pregnancy, n (%)	0	0	0	1 (2.0)	0	1 (1.0)	0
Exposure to a Known Human Teratogen in Pregnancy, n (%)	0	0	0	1 (2.0)	0	1 (1.0)	0
Dose and Frequency of Tofacitinib, n (%) 10 mg per day 5 mg per day Other[q]	 3 (75.0) 0 1 (25.0)	 1 (14.3) 0 6 (85.7)	 4 (36.4) 0 7 (63.6)	 ---- ---- ----	 ---- ---- ----	 ---- ---- ----	 ---- ---- ----
Gestational Timing of Tofacitinib Use in Pregnancy[r] - LMP to < DOC only[s] - 1st Trimester only - 1st and 2nd Trimesters only - 1st and 3rd Trimesters only - 1st, 2nd, and 3rd Trimesters - 2nd Trimester only - 2nd and 3rd Trimesters only	 0 3 (100.0) 0 0 0 0 0	 0 0 0 0 6 (100.0) 0 0	 0 3 (33.3) 0 0 6 (66.7) 0 0	 ---- ---- ---- ---- ---- ---- ----	 ---- ---- ---- ---- ---- ---- ----	 ---- ---- ---- ---- ---- ---- ----	 ---- ---- ---- ---- ---- ---- ----

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
- 3rd Trimester only	0		0	----	----	----	----
Prenatal Diagnostic Tests Performed Prior to Enrollment, n (%)							
-Ultrasound Level 1	3 (75.0)	5 (71.4)	8 (72.7)	39 (79.6)	37 (72.5)	76 (76.0)	83 (83.0)
-Ultrasound Level 2	0	0	0	2 (4.1)	4 (7.8)	6 (6.0)	8 (8.0)
-Chorionic villus sampling (CVS)	0	0	0	0	0	0	0
-Amniocentesis	0	0	0	0	0	0	0
Prenatal Diagnostic Tests Performed Anytime in Pregnancy, n (%)							
-Ultrasound Level 1	3 (75.0)	7 (100.0)	10 (90.9)	48 (98.0)	50 (98.0)	98 (98.0)	97 (97.0)
-Ultrasound Level 2	1 (25.0)	6 (85.7)	7 (63.6)	43 (87.8)	47 (92.2)	90 (90.0)	94 (94.0)
-Chorionic villus sampling (CVS)	0	0	0	1 (2.0)	0	1 (1.0)	0
-Amniocentesis	0	0	0	0	1 (2.0)	1 (1.0)	0

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)
Maternal Comorbidity, n (%)							
-Ankylosing Spondylitis	0	0	0	1 (2.0)	0	1 (1.0)	0
-Asthma	0	0	0	3 (6.1)	1 (2.0)	4 (4.0)	0
-Autoimmune Disease, Other	0	0	0	2 (4.1)	5 (9.8)	7 (7.0)	0
-Crohn's Disease	0	0	0	2 (4.1)	0	2 (2.0)	0
-Depression	2 (50.0)	1 (14.3)	3 (27.3)	8 (16.3)	9 (17.6)	17 (17.0)	0
-Chronic Hypertension	1 (25.0)	0	1 (9.1)	2 (4.1)	0	2 (2.0)	2 (2.0)
-Lupus	0	0	0	3 (6.1)	0	3 (3.0)	0
-Multiple Sclerosis	0	0	0	0	0	0	0
-Psoriasis	0	0	0	1 (2.0)	1 (2.0)	2 (2.0)	0
-Psychiatric Condition	0	0	0	0	1 (2.0)	1 (1.0)	0
-Thyroid Dysfunction	0	0	0	1 (2.0)	0	1 (1.0)	0

N: Number of participants with outcome.

a. Based on four-factor Hollingshead categories incorporating maternal and paternal education and occupation; highest socioeconomic status category = 1; lowest socioeconomic status category = 5.Participants with Hollingshead score missing- Tofacitinib Exposed RA/PsA group: 1
b. Participants with maternal pre-pregnancy weight missing - Tofacitinib Exposed RA/PsA group: 1
c. Participants with maternal pre-pregnancy BMI missing - Tofacitinib Exposed RA/PsA group: 1
d. Participants with household income missing - Diseased Unexposed RA/PsA group: 1
e. Participants with paternal age at birth missing - Diseased Unexposed RA/PsA group: 3, Diseased Unexposed UC group: 4, Non-Diseased Unexposed group: 4
f. Includes molar pregnancies, blighted ovum, and ectopic pregnancies.
g. RA 1: Maternal report of disease severity score expressed as the HAQ-DI summary score; possible score ranges from 0-3 with higher score representing higher severity/disability
h. RA 2: Maternal report of experience of disease-related pain; possible score 0-100 with higher score indicating more pain
i. RA 3: Maternal report of how overall illness affects her; possible score 0-100 with higher score indicating more effect
j. Participants with Intake Rheumatic score missing- Tofacitinib Exposed UC: 7, Diseased Unexposed RA/PsA: 1, Diseased Unexposed UC: 50
k. Participants with 2nd Trimester (20 week) Rheumatic score missing- Tofacitinib Exposed RA/PsA group: 3, Tofacitinib Exposed UC: 7, Diseased Unexposed RA/PsA: 9, Diseased Unexposed UC: 50

Table 5. Maternal Characteristics of Pregnancies Enrolled in the Tofacitinib Pregnancy Exposure Registry

	Tofacitinib Exposed RA/PsA (N = 4) n (%)	Tofacitinib Exposed UC (N = 7) n (%)	Tofacitinib Exposed Total (N = 11) n (%)	Diseased Unexposed RA/PsA (N = 49) n (%)	Diseased Unexposed UC (N = 51) n (%)	Diseased Unexposed Total (N = 100) n (%)	Non-Diseased Unexposed (N = 100) n (%)

l. Participants with 3rd Trimester (32 week) Rheumatic score missing- Tofacitinib Exposed RA/PsA group: 3, Tofacitinib Exposed UC: 7, Diseased Unexposed RA/PsA: 13, Diseased Unexposed UC: 50
m. SBDIQ: Short IBD Questionnaire, an instrument to measure quality of life in participants with IBD (CD/UC); possible score 0-7 with lower score indicating poor quality of life.
n. Participants with Intake UC score missing- Tofacitinib Exposed RA/PsA group: 4, Diseased Unexposed RA/PsA: 48, Diseased Unexposed UC: 2
o. Participants with Intake UC score missing- Tofacitinib Exposed RA/PsA group: 4, Tofacitinib Exposed UC: 2, Diseased Unexposed RA/PsA: 48, Diseased Unexposed UC: 13
p. Participants with Intake UC score missing- Tofacitinib Exposed RA/PsA group: 4, Tofacitinib Exposed UC: 1, Diseased Unexposed RA/PsA: 48, Diseased Unexposed UC: 10
q. Other doses: One participant took 11 mg per day, and eight participants took 10 mg two times per day
r. Participants with gestational timing of Tofacitinib in pregnancy missing- Tofacitinib Exposed RA/PsA group: 1, Tofacitinib Exposed UC group: 1
s. Standard definition of the 1st trimester is [0, 11] weeks' post conception, the 2nd trimester is (11, 24] weeks' post conception, the 3rd trimester is (24, 43] weeks' post conception. In this table, the 1st trimester includes last menstrual period (LMP) to date of conception (DOC), i.e., if a participant is exposed in both LMP to DOC and the 1st trimester, she will be in the category of '1st Trimester'"

10.3. Outcome Data

Pregnancy outcome data are presented in Table 6 of this report. The proportion of pregnancies ending in at least one live birth was lower in the tofacitinib-exposed cohort 8/11 (72.7%), compared to the diseased unexposed cohort 88/100 (88.0%), and the non-diseased unexposed cohort 92/100 (92.0%). No stillbirths or elective terminations were reported in any of the cohort groups. Losses-to-follow-up occurred in 2/11 (18.2%) in the tofacitinib-exposed cohort, compared to 5/100 (5.0%) and 7/100 (7.0%) in the two unexposed comparison cohorts, respectively.

Table 6. Pregnancy Outcome

	Tofacitinib Exposed RA/PsA (N = 4) n/N' (%)	Tofacitinib Exposed UC (N = 7) n/N' (%)	Tofacitinib Exposed Total (N = 11) n/N' (%)	Diseased Unexposed RA/PsA (N = 49) n/N' (%)	Diseased Unexposed UC (N = 51) n/N' (%)	Diseased Unexposed Total (N = 100) n/N' (%)	Non-Diseased Unexposed (N = 100) n/N' (%)
Live birth	1/4 (25.0)	7/7 (100.0)	8/11 (72.7)	43/49 (87.8)	45/51 (88.2)	88/100 (88.0)	92/100 (92.0)
Twin	0/1 (0.0)	0/7 (0.0)	0/8 (0.0)	2/43 (4.7)	1/45 (2.2)	3/88 (3.4)	2/92 (2.2)
Twin with like sex	----	----	----	1/2 (50.0)	1/1 (100.0)	2/3 (66.7)	1/2 (50.0)
Sex (male)	----	----	----	1/1 (100.0)	0/1 (0.0)	1/2 (50.0)	0/1 (0.0)
Twin with non-like sex	----	----	----	0/2 (0.0)	0/1 (0.0)	0/3 (0.0)	0/2 (0.0)
Twin with only one surviving	----	----	----	1/2 (50.0)	0/1 (0.0)	1/3 (33.3)	1/2 (50.0)
Sex (male)	----	----	----	1/1 (100.0)	----	1/1 (100.0)	0/1 (0.0)
Singleton	1/1 (100.0)	7/7 (100.0)	8/8 (100.0)	41/43 (95.3)	44/45 (97.8)	85/88 (96.6)	90/92 (97.8)
Sex (male)	0/1 (0.0)	6/7 (85.7)	6/8 (75.0)	23/41 (56.1)	27/44 (61.4)	50/85 (58.8)	46/90 (51.1)
Cesarean	1/1 (100.0)	3/7 (42.9)	4/8 (50.0)	17/43 (39.5)	13/45 (28.9)	30/88 (34.1)	12/92 (13.0)
Spontaneous Abortion[a]	1/4	0/7	1/11	3/49	4/51	7/100	1/100
Spontaneous Abortion-Twins	0/1	----	0/1	0/3	0/4	0/7	0/1
Stillbirth	0/4 (0.0)	0/7 (0.0)	0/11 (0.0)	0/49 (0.0)	0/51 (0.0)	0/100	0/100
Termination	0/4 (0.0)	0/7 (0.0)	0/11 (0.0)	0/49 (0.0)	0/51 (0.0)	0/100	0/100
Social	----	----	----	----	----	----	----
Medical	----	----	----	----	----	----	----
Lost-to-Follow-Up[b]	2/4 (50.0)	0/7 (0.0)	2/11 (18.2)	3/49 (6.1)	2/51 (3.9)	5/100 (5.0)	7/100 (7.0)
No Contact	2/2 (100.0)	----	2/2 (100.0)	3/3 (100.0)	0/2 (0.0)	3/5 (60.0)	5/7 (71.4)
Withdrew	0/2 (0.0)	----	0/2 (0.0)	0/3 (0.0)	2/2 (100.0)	2/5 (40.0)	2/7 (28.6)

Table 6. Pregnancy Outcome

	Tofacitinib Exposed RA/PsA (N = 4) n/N' (%)	Tofacitinib Exposed UC (N = 7) n/N' (%)	Tofacitinib Exposed Total (N = 11) n/N' (%)	Diseased Unexposed RA/PsA (N = 49) n/N' (%)	Diseased Unexposed UC (N = 51) n/N' (%)	Diseased Unexposed Total (N = 100) n/N' (%)	Non-Diseased Unexposed (N = 100) n/N' (%)

a. Left Truncation Accounted Spontaneous Abortion Rate in Table 5.3
b. One pregnancy in the Non-Diseased Unexposed cohort had twin outcome.
N: Number of participants with pregnancy outcome
n/N' (%) is either out of total N or % of the N' subcategories under the live birth, spontaneous abortion, stillbirth, termination or lost to follow-up rows.

10.4. Main Results

Major Birth Defects:

One pregnancy of eight ending in at least one live birth in the tofacitinib-exposed cohort resulted in an infant with a major birth defect (12.5%, 95% CI 0.66, 48.01). There were 3 of 88 livebirths with defects (3.4%, 95% CI 0.91, 8.96) in the diseased unexposed cohort, and 8 of 92 (8.7%, 95% CI 4.16, 15.81) in the non-diseased comparison cohort. Inclusion of pregnancy losses in the numerators/denominators, as appropriate, resulted in 1/9 (11.1%, 95% CI 0.56, 43.86) in the tofacitinib-exposed cohort vs. 4/95 (4.2%, 95% CI 1.36, 9.81) in the diseased unexposed cohort and 9/93 (9.7%, 95% CI 4.86, 17.01), in the non-diseased comparison cohort (Table 7). The external MACDP population reference rate was 3.0% (Table 7).

The specific major structural birth defect identified in the one tofacitinib-exposed pregnancy was chordee with first degree hypospadias (Annex 2 Additional Data Table 32).

Table 7. Major Birth Defects in Tofacitinib-Exposed Pregnancies and Comparison Cohort Pregnancies

	Tofacitinib Exposed RA/PsA n/N' (%)	Tofacitinib Exposed UC n/N' (%)	Tofacitinib Exposed Total n/N' (%)	Diseased Unexposed RA/PsA n/N' (%)	Diseased Unexposed UC n/N' (%)	Diseased Unexposed Total n/N' (%)	Non-Diseased Unexposed n/N' (%)	MACDP Reference Rate[b]
Number of pregnancies ending with at least one live born infant with a major birth defect[a]	0/1 (0.0) [0.00, 95.00]	1/7 (14.3) [0.76, 53.01]	1/8 (12.5) [0.66, 48.01]	1/43 (2.3) [0.16, 10.91]	2/45 (4.4) [0.76, 13.91]	3/88 (3.4) [0.91, 8.96]	8/92 (8.7) [4.16, 15.81]	--
Number of all pregnancies (excluding lost-to-follow-up) with major birth defects[a]	0/2 (0.0) [0.00, 77.64]	1/7 (14.3) [0.76, 53.01]	1/9 (11.1) [0.56, 43.86]	2/46 (4.3) [0.76, 13.61]	2/49 (4.1) [0.71, 12.81]	4/95 (4.2) [1.36, 9.81]	9/93 (9.7) [4.86, 17.01]	3.0

a A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

b MACDP (Metropolitan Atlanta Congenital Defects Program). Morbidity and Mortality Weekly Report (MMWR) January 11, 2008 / 57(01):1-5. To be included in the numerator for calculation of rate in MACDP, live born or stillborn infants with defects must have a gestational age of at least 20 weeks; electively terminated

Pattern of Minor Malformations:

Three (42.9%) of the 7 infants in the tofacitinib-exposed cohort, 55/90 (61.1%) in the diseased unexposed cohort, and 53/93 (57.0%) in the non-diseased unexposed cohort who were eligible for the study-related dysmorphology exam received the exam. The numbers of infants who were examined and who had 3 or more minor malformations were 1/3 (33.3%, 95% CI 4.34, 84.65) in the tofacitinib-exposed cohort, 4/55 (7.3%, 95% CI 2.75, 17.87) in the diseased unexposed cohort, and 3/53 (5.7%, 95% CI 1.84, 16.13) in the non-diseased unexposed cohort. Among the 3 infants in the tofacitinib-exposed group who received the dysmorphology physical examination, there were no infants with a pattern of 3 or minor malformations identified (Table 8).

Table 8. Number of Infants with Three or More or a Pattern of Minor Malformations among All Infants That Received the Dysmorphological Examination[a]

	Tofacitinib Exposed RA/PsA n/N (%)	Tofacitinib Exposed UC n/N (%)	Tofacitinib Exposed Total n/N (%)	Diseased Unexposed RA/PsA n/N (%)	Diseased Unexposed UC n/N (%)	Diseased Unexposed Total n/N (%)	Non-Diseased Unexposed n/N (%)
Number of infants who received the Exam/Number of infants eligible for Exam	1/1 (100.0) [100.00, 100.00]	2/6 (33.3) [8.39, 73.19]	3/7 (42.9) [14.37, 77.02]	27/44 (61.4) [46.19, 74.61]	28/46 (60.9) [46.05, 73.93]	55/90 (61.1) [50.56, 70.72]	53/93 (57.0) [46.63, 66.77]
Number of infants examined with at least 3 or more of any minor malformations[b]	1/1 (100.0) [100.00, 100.00]	0/2 (0.0) [0.00, 0.00]	1/3 (33.3) [4.34, 84.65]	3/27 (11.1) [3.61, 29.45]	1/28 (3.6) [0.50, 21.46]	4/55 (7.3) [2.75, 17.87]	3/53 (5.7) [1.84, 16.13]
Number of infants examined with a pattern of 3 or more minor malformations[c]	0/1 (0.0) [0.00, 0.00]	0/2 (0.0) [0.00, 0.00]	0/3 (0.0) [0.00, 0.00]	0/27 (0.0) [0.00, 0.00]	0/28 (0.0) [0.00, 0.00]	0/55 (0.0) [0.00, 0.00]	0/53 (0.0) [0.00, 0.00]

[a].95% CI estimated using the generalized estimating equations (GEE) approach, logit-binomial link and independent working correlation.

b.Includes singletons and multiples who received the dysmorphological exam

c.Includes singletons and multiples who received the dysmorphological exam for consideration of pattern; however, co-twins with the same three or more minor structural defects could not constitute a pattern on their own

Spontaneous Abortion:

There was 1 spontaneous abortion reported in the tofacitinib-exposed group, 7 in the disease-matched unexposed comparison group, and 1 in the non-diseased unexposed comparison group. The left-truncation accounted Fleming-Harrington rates were 28.3% (95% CI 4.6%, 90.6%); 17.8% (95% CI 8.0%, 37.0%); and 6.9% (95% CI 1.0%, 39.8%), in each cohort respectively (Table 9).

Table 9. Spontaneous Abortion (SAB) Among Women with at Least One Day of Follow-Up

	Tofacitinib Exposed RA/PsA (N = 2)	Tofacitinib Exposed UC (N = 7)	Tofacitinib Exposed Total (N = 9)	Diseased Unexposed RA/PsA (N = 48)	Diseased Unexposed UC (N = 49)	Diseased Unexposed Total (N = 97)	Non-Diseased Unexposed (N = 97)
Number of SAB Events [a]	1	0	1	3	4	7	1
Left Truncation Accounted SAB Rate [b,c,d]	63.2% [13.1%, 99.9%]	----	28.3% [4.6%, 90.6%]	14.7% [4.1%, 45.4%]	19.2% [6.8%, 47.8%]	17.8% [8.0%, 37.0%]	6.9% [1.0%, 39.8%]

a.In pregnancies involving multiples (twins/triplets) with one or more of the outcomes ending in spontaneous abortion, when there are no live births, the pregnancy is counted as one spontaneous abortion event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.

b.SAB rate computed using Fleming-Harrington estimate at 20 weeks' gestation, accounting for left truncation because women can enroll at various times in gestation.

c.Eight lost-to-follow-up cases were excluded due to having zero days of follow-up: 2 Tofacitinib Exposed RA/PsA, 1 Unexposed RA/PsA, 2 Unexposed UC, 3 Non-Diseased Unexposed.

d.Earliest gestational age at enrollment (weeks): Tofacitinib Exposed RA/PsA 7.4, Tofacitinib Exposed UC 6.4, Unexposed RA/PsA 4.9, Unexposed UC 5.7, Non-Diseased Unexposed 5.7.

N: Number of participants enrolled and exposed prior to 20 weeks' gestation and with follow up.

Elective Termination:

There were no elective terminations in any of the cohort groups.

Stillbirth:

There were no stillbirths in any of the cohort groups.

Preterm Delivery:

There were 2 pregnancies resulting in preterm delivery among 8 ending in live born singleton infants in the tofacitinib-exposed cohort. There were 7 preterm deliveries among 87 pregnancies in the diseased unexposed cohort, and 4 preterm deliveries among

93 pregnancies in the non-diseased unexposed cohort. The corresponding Fleming-Harrington rates were 23.5% (95% CI 6.5%, 65.8%), 8.2% (95% CI 4.0%, 16.4%), and 4.4% (95% CI 1.7%, 11.2%), in each cohort respectively (Table 10).

Table 10. Preterm Delivery (PTD) Among Pregnancies Enrolled and Exposed prior to 37 Weeks Gestation and Ending in Live Birth or Lost-To-Follow-Up with at Least One Day Follow-Up (Multiple Births Excluded)

	Tofacitinib Exposed RA/PsA (N = 1)	Tofacitinib Exposed UC (N = 7)	Tofacitinib Exposed Total (N = 8)	Diseased Unexposed RA/PsA (N = 43)	Diseased Unexposed UC (N = 44)	Diseased Unexposed (N = 87)	Non-Diseased Unexposed (N = 93)
Number of PTD (n)[a]	0	2	2	3	4	7	4
Left Truncation Accounted PTD Rate[b]	0.0%	26.6% [7.4%, 71.1%]	23.5% [6.5%, 65.8%]	7.2% [2.4%, 20.6%]	9.0% [3.5%, 22.2%]	8.2% [4.0%, 16.4%]	4.4% [1.7%, 11.2%]

a.Computed using Fleming-Harrington estimate at 37 weeks gestation.

b.Eight cases were excluded due to having zero days of follow-up: 2 Tofacitinib Exposed RA/PsA, 1 Unexposed RA/PsA, 2 Unexposed UC, 3 Non-Diseased Unexposed (including 1 LTFU twin case).

N: Number of participants enrolled and exposed prior to 37 weeks' gestation, ending in live birth singleton or LTFU with at least one day follow-up.

Small for Gestational Age (SGA) and Small for Age on Postnatal Growth:

By definition, approximately 10% of infants are expected to meet criteria for small for gestational age at delivery due to the normal distribution of infant size. In the tofacitinib-exposed cohort, 2/8 (25.0%, 95% CI 4.46, 61.16) were SGA on birth weight, none were SGA on birth length, and 1/6 (16.7%, 95% CI 0.86, 59.06) was SGA on birth head circumference. One of these infants was small on both weight and head circumference. The percentages in the comparator cohorts were at or below the 10th centile for all three measures (Table 11).

At 1-year follow-up, 1/5 (20.0%, 95% CI 1.01, 66.51) infants was small on postnatal weight in the tofacitinib-exposed cohort, but there were no infants small for postnatal growth on length or head circumference. Similarly, in both comparison groups, the proportion of small infants at about 1 year exceeded the 10 percent expected in the general population on weight but did not on length, and only slightly exceeded the cutoff on head circumference in the non-diseased cohort (Table 12).

Table 11. Small for Gestational Age (SGA) at Birth Among Live Born Infants (Multiple Pregnancies Excluded)[a]

	Tofacitinib Exposed RA/PsA (N = 1) n/N' (%)	Tofacitinib Exposed UC (N = 7) n/N' (%)	Tofacitinib Exposed Total (N = 8) n/N' (%)	Diseased Unexposed RA/PsA (N = 41) n/N' (%)	Diseased Unexposed UC (N = 44) n/N' (%)	Diseased Unexposed Total (N = 85) n/N' (%)	Non-Diseased Unexposed (N = 90) n/N' (%)
SGA on Weight	0/1 (0.0) [0.00, 95.00]	2/7 (28.6) [5.11, 66.96]	2/8 (25.0) [4.46, 61.16]	3/41 (7.3) [1.91, 18.61]	3/44 (6.8) [1.81, 17.41]	6/85 (7.1) [2.96, 14.06]	6/90 (6.7) [2.76, 13.31]
SGA on Length	0/1 (0.0) [0.00, 95.00]	0/6 (0.0) [0.00, 39.30]	0/7 (0.0) [0.00, 34.82]	1/40 (2.5) [0.16, 11.71]	1/41 (2.4) [0.16, 11.41]	2/81 (2.5) [0.46, 7.91]	3/89 (3.4) [0.91, 8.86]
SGA on Occipitofrontal Circumference (OFC)	0/1 (0.0) [0.00, 95.00]	1/5 (20.0) [1.01, 66.51]	1/6 (16.7) [0.86, 59.06]	3/34 (8.8) [2.31, 22.16]	4/37 (10.8) [3.56, 24.01]	7/71 (9.9) [4.46, 18.51]	8/81 (9.9) [4.71, 17.86]
SGA on weight and/or length, but not OFC	0/1 (0.0) [0.00, 95.00]	0/6 (0.0) [0.00, 39.30]	0/7 (0.0) [0.00, 34.80]	1/38 (2.6) [0.16, 12.26]	1/39 (2.6) [0.20, 12.00]	2/77 (2.6) [0.46, 8.31]	3/87 (3.4) [0.90, 9.10]
SGA on weight and/or length, and OFC	0/1 (0.0) [0.00, 95.00]	1/6 (16.7) [0.86, 59.06]	1/7 (14.3) [0.76, 53.01]	1/38 (2.6) [0.16, 12.26]	1/40 (2.5) [0.16, 11.71]	2/78 (2.6) [0.46, 8.21]	2/87 (2.3) [0.41, 7.36]

a.SGA defined as ≤10th centile for gestational age and sex.

N: Number of singleton live born infants.

N' at each category of growth measurement: Number of live born singletons for whom the specific growth measurement is available.

Table 12. Postnatal Growth at Approximately One Year - Percentile ⩽10th (Multiple Births Excluded)

	Tofacitinib Exposed RA/PsA (N = 1) n/N' (%)	Tofacitinib Exposed UC (N = 6) n/N' (%)	Tofacitinib Exposed Total (N = 7) n/N' (%)	Diseased Unexposed RA/PsA (N = 38) n/N' (%)	Diseased Unexposed UC (N = 42) n/N' (%)	Diseased Unexposed Total (N = 80) n/N' (%)	Non-Diseased Unexposed (N = 88) n/N' (%)
Weight ≤10th centile[a]	0/1 (0.0) [0.00, 95.00]	1/4 (25.0) [1.26, 75.76]	1/5 (20.0) [1.01, 66.51]	6/31 (19.4) [8.26, 35.96]	3/29 (10.3) [2.71, 25.61]	9/60 (15.0) [7.61, 25.71]	14/61 (23.0) [13.71, 34.71]
Length ≤10th centile[a]	0/1 (0.0) [0.00, 95.00]	0/4 (0.0) [0.00, 52.71]	0/5 (0.0) [0.00 ,45.07]	1/31 (3.2) [0.21, 14.86]	0/29 (0.0) [0.00, 9.81]	1/60 (1.7) [0.11, 7.91]	2/61 (3.3) [0.91, 8.86]
Occipitofrontal Circumference ≤10th centile[a]	0/1 (0.0) [0.00, 95.00]	0/4 (0.0) [0.00, 52.71]	0/5 (0.0) [0.00, 45.07]	0/31 (0.0) [0.00, 9.21]	1/29 (3.4) [0.21, 15.81]	1/60 (1.7) [0.11, 7.91]	6/59 (10.2) [4.71, 17.86]

a.≤10th centile for chronological age. Age adjusted if child was less than 12 months, unadjusted if ≥12 months. Measurements were taken at 12 months of age +/- 3 months

N: Number of singleton infants who had reached one year of age.

Serious or Opportunistic Infections, and Malignancies:

There were no serious or opportunistic infections in the tofacitinib-exposed cohort group in infants followed through the first year of life, compared to 7.8% in the diseased unexposed comparison and 4.3% in the non-diseased unexposed cohort (Table 13).

No infant malignancies up to one year of age were reported in any of the cohort groups (Table 14).

Table 13. Postnatal Events - Serious or Opportunistic Infections in Infants up to One Year of Age (Including Infants from Multiple Births)

	Tofacitinib Exposed RA/PsA (N = 1) n/N' (%)	Tofacitinib Exposed UC (N = 7) n/N' (%)	Tofacitinib Exposed Total (N = 8) n/N' (%)	Diseased Unexposed RA/PsA (N = 44) n/N' (%)	Diseased Unexposed UC (N = 46) n/N' (%)	Diseased Unexposed Total (N = 90) n/N' (%)	Non-Diseased Unexposed (N = 93) n/N' (%)
Serious or Opportunistic Infections in Infants up to One Year of Age (Including Infants from Multiple Births)	0/1 (0.0) [0.00, 0.00]	0/7 (0.0) [0.00, 0.00]	0/8 (0.0) [0.00, 0.00]	4/44 (9.1) [3.45, 21.88]	3/46 (6.5) [2.11, 18.39]	7/90 (7.8) [3.75, 15.45]	4/93 (4.3) [1.62, 10.91]

95% CI estimated using the generalized estimating equations (GEE) approach, logit-binomial link and independent working correlation.

N: Number of live born infants.

% = (n/N) * 100; N': Number of live born infants with the event yes/no and event timing information available.

Table 14. Postnatal Events - Malignancies in Infants up to One Year of Age (Including Infants from Multiple Births)

	Tofacitinib Exposed RA/PsA (N = 1) n/N' (%)	Tofacitinib Exposed UC (N = 7) n/N' (%)	Tofacitinib Exposed Total (N = 8) n/N' (%)	Diseased Unexposed RA/PsA (N = 44) n/N' (%)	Diseased Unexposed UC (N = 46) n/N' (%)	Diseased Unexposed Total (N = 90) n/N' (%)	Non-Diseased Unexposed (N = 93) n/N' (%)
Malignancies in Infants up to One Year of Age (Including Infants from Multiple Births)	0/1 (0.0) [0.00, 0.00]	0/7 (0.0) [0.00, 0.00]	0/8 (0.0) [0.00, 0.00]	0/44 (0.0) [0.00, 0.00]	0/46 (0.0) [0.00, 0.00]	0/90 (0.0) [0.00, 0.00]	0/93 (0.0) [0.00, 0.00]

95% CI estimated using the generalized estimating equations (GEE) approach, logit--binomial link and independent working correlation.

N: Number of live born infants.

% = (n/N) * 100; N': Number of live born infants with the event yes/no and event timing information available.

10.5. Other Analyses

10.5.1. Sensitivity Analyses for the Primary Outcome

The one case of methotrexate exposure occurred in the diseased unexposed cohort, so exclusion of that case did not result in a change to the birth prevalence of major birth defects in the tofacitinib-exposed cohort (Table 15). Similarly, the one defect reported in the tofacitinib-exposed cohort was not due to a genetic or chromosomal anomaly (Table 16) and there were no cases of prenatal diagnosis prior to enrollment in the tofacitinib-exposed cohort (Table 17 and Table 18).

Table 15. Major Birth Defects Excluding Those with Methotrexate Exposure

	Tofacitinib Exposed RA/PsA n/N' (%)	Tofacitinib Exposed UC n/N' (%)	Tofacitinib Exposed Total n/N' (%)	Diseased Unexposed RA/PsA n/N' (%)	Diseased Unexposed UC n/N' (%)	Diseased Unexposed Total n/N' (%)	Non-Diseased Unexposed n/N' (%)
Number of pregnancies ending with at least one live born infant with a major birth defect	0/1 (0.0) [0.00, 95.00]	1/7 (14.3) [0.76, 53.01]	1/8 (12.5) [0.66, 48.01]	1/42 (2.4) [0.16, 11.16]	2/45 (4.4) [0.81, 14.51]	3/87 (3.4) [0.91, 9.06]	8/92 (8.7) [4.16, 15.81]
Number of all pregnancies (excluding lost-to-follow-up) with major birth defects	0/2 (0.0) [0.00, 77.64]	1/7 (14.3) [0.76, 53.01]	1/9 (11.1) [0.56, 43.86]	2/45 (4.4) [0.81, 14.51]	2/49 (4.1) [0.71, 12.81]	4/94 (4.3) [1.41, 9.91]	9/93 (9.7) [4.86, 17.01]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

Table 16. Major Birth Defects Excluding Defects Thought to Be of Chromosomal or Genetic Origin

	Tofacitinib Exposed RA/PsA n/N' (%)	Tofacitinib Exposed UC n/N' (%)	Tofacitinib Exposed Total n/N' (%)	Diseased Unexposed RA/PsA n/N' (%)	Diseased Unexposed UC n/N' (%)	Diseased Unexposed Total n/N' (%)	Non-Diseased Unexposed n/N' (%)
Number of pregnancies ending with at least one live born infant with a major birth defect	0/1 (0.0) [0.00, 95.00]	1/7 (14.3) [0.76, 53.01]	1/8 (12.5) [0.66, 48.01]	1/43 (2.3) [0.16, 10.91]	1/44 (2.3) [0.16, 10.66]	2/87 (2.3) [0.41, 7.36]	7/91 (7.7) [3.46, 14.61]
Number of all pregnancies (excluding lost-to-follow-up) with major birth defects	0/2 (0.0) [0.00, 77.64]	1/7 (14.3) [0.76, 53.01]	1/9 (11.1) [0.56, 43.86]	1/45 (42.2) [0.16, 10.46]	1/48 (2.1) [0.11, 9.81]	2/93 (2.2) [0.41, 6.91]	7/91 (7.7) [3.46, 14.61]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

Table 17. Major Birth Defects Among Pregnancies That Had Prenatal Diagnostic Testing Prior to Enrollment[a]

	Tofacitinib Exposed RA/PsA n/N' (%)	Tofacitinib Exposed UC n/N' (%)	Tofacitinib Exposed Total n/N' (%)	Diseased Unexposed RA/PsA n/N' (%)	Diseased Unexposed UC n/N' (%)	Diseased Unexposed Total n/N' (%)	Non-Diseased Unexposed n/N' (%)
Number of pregnancies ending with at least one live born infant with a major birth defect	----	----	----	0/2 (0.0) [0.00,77.64]	0/3 (0.0) [0.00,63.16]	0/5 (0.0) [0.00,45.07]	0/7 (0.0) [0.00,34.82]
Number of all pregnancies (excluding lost-to-follow-up) with major birth defects	----	----	----	0/2 (0.0) [0.00,77.64]	0/3 (0.0) [0.00,63.16]	0/5 (0.0) [0.00,45.07]	0/7 (0.0) [0.00,34.82]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

a.Prenatal diagnostic tests include Ultrasound Level 2, Chorionic villus sampling (CVS), and Amniocentesis.

Table 18. Major Birth Defects among Pregnancies That Did Not Have Prenatal Diagnostic Testing Prior to Enrollment[a]

	Tofacitinib Exposed RA/PsA n/N' (%)	Tofacitinib Exposed UC n/N' (%)	Tofacitinib Exposed Total n/N' (%)	Diseased Unexposed RA/PsA n/N' (%)	Diseased Unexposed UC n/N' (%)	Diseased Unexposed Total n/N' (%)	Non-Diseased Unexposed n/N' (%)
Number of pregnancies ending with at least one live born infant with a major birth defect	0/1 (0.0) [0.00, 95.00]	1/7 (14.3) [0.76, 53.01]	1/8 (12.5) [0.66, 48.01]	1/41 (2.4) [0.16, 11.41]	2/42 (4.8) [0.81, 14.81]	3/83 (3.6) [0.96, 9.51]	8/85 (9.4) [4.51, 17.06]
Number of all pregnancies (excluding lost-to-follow-up) with major birth defects	0/2 (0.0) [0.00, 77.64]	1/7 (14.3) [0.76, 53.01]	1/9 (11.1) [0.56, 43.86]	2/44 (4.5) [0.81, 14.81]	2/46 (4.3) [0.76, 13.61]	4/90 (4.4) [1.46, 10.36]	9/86 (10.5) [5.26, 18.31]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

a.Prenatal diagnostic tests include Ultra Sound Level 2, Chorionic villus sampling (CVS), and Amniocentesis.

10.6. Adverse Events / Adverse Reactions

No study adverse events (AEs) with explicit attribution to Xeljanz were reported (defined per the patient population and study period specified in the protocol); however, one participant stated they discontinued the drug due to ineffectiveness Explicit attribution is not inferred by a temporal relationship between drug administration and an AE but was based on a definite statement of causality by a healthcare provider for a study participant or a study participant linking drug administration to the AE.

11. DISCUSSION

Literature Review

Risks for Adverse Pregnancy Outcomes Associated with Maternal Rheumatoid Arthritis (RA) and Psoriatic Arthritis (PsA)

There has been no indication in the published literature of an increased risk of major birth defects overall, spontaneous abortion, or stillbirth in women with RA (Barnabe et al, 2011; Skomsvoll et al, 2000; Reed et al, 2006; de Man et al, 2009; Norgaard et al, 2010; Lin et al, 2010; Bowden et al, 2001, Wallenius et al, 2014).

However, studies consistently report increased risks for small for gestational age infants in pregnancies of women with RA. Lin et al (2010) found a 1.20 adjusted OR (95% CI 1.05, 1.38) of being small for gestational age in 1,912 infants born to mothers with RA compared to 9,560 matched comparison mothers in Taiwan. In the UK, Bowden et al (2001) examined outcomes in 103 women with RA or undifferentiated inflammatory polyarthritis and matched controls, and found that babies born to women with arthritis had significantly lower mean birth weight (about 200 grams on average), especially in those born to mothers with active disease. Norgaard et al (2010) used national data from Denmark and Sweden 1994-2006 and measured the incidence of adverse pregnancy outcomes in 1,199 pregnancies among women with RA compared to 870,380 women without RA. In that study, women with RA compared to women without RA had an adjusted OR of 1.56 (95% CI 1.20, 2.01) for having an infant that was SGA at birth.

With respect to preterm delivery, in the Norgaard et al (2010) study, women with RA compared to women without RA had an adjusted OR of 1.44 (95% CI 1.14, 1.82) for delivery between 32 and 36 weeks' gestation and had a non-significant adjusted OR of 1.55 (95% CI 0.97, 2.47) for delivery before 32 weeks' gestation. In a smaller study reported by Reed et al (2006), the adjusted relative risk of preterm delivery was 1.78 (95% CI 1.21, 2.60) in 243 women with RA compared to 2,559 controls in Washington State. Using a patient registry linked to the Medical Birth Registry of Norway, Wallenius et al (2014) evaluated outcomes in 1,496 women with RA and 625,642 reference deliveries from the general population between 1998 and 2009. Preterm delivery was more frequent in RA patients in the first pregnancy (adjusted OR 1.5, 95% CI 1.1, 2.0).

In women with PsA, Remaeus et al (2019) used Swedish population-based data to compare outcomes in 541 singleton pregnancies occurring in 330 women with PsA to 40, 944 pregnancies in 25,594 women without PsA and found increased risks of preterm birth (adjusted OR 1.63; 95% CI 1.17, 2.28), and elective and emergency caesarean deliveries (adjusted OR 1.47; 95% CI 1.10,1.97 and adjusted OR 1.43; 95% CI 1.08,1.88, respectively) compared with non-PsA pregnancies. There were no statistical differences between groups for pre-eclampsia, or small for gestational age, and no differences were identified for stillbirth or neonatal death.

Meissner et al (2021) performed a systematic review covering 2,332 pregnancies in women with PsA. Adjusted analyses of adverse pregnancy outcomes did not show an increased risk for gestational diabetes, SGA, or low birth weight in pregnant women with PsA in relation to their respective comparator groups. However, there were signals for a higher incidence of pre-eclampsia, elective caesarean delivery, and preterm birth risk.

Finally, across inflammatory arthritis conditions, Skomsvoll et al (2000) noted a significantly higher rate of delivery by caesarean section in women with specified inflammatory arthritis compared to the general population of Norway 1987-1995 (adjusted OR 1.51, 95% CI 1.36, 1.68) as well as an increased risk for preeclampsia (adjusted OR 1.28, 95% CI 1.05, 1.56).

Risks for Adverse Pregnancy Outcomes Associated with Maternal Ulcerative Colitis (UC) and Inflammatory Bowel Disease (IBD) Overall

Ban et al (2014) compared 1,703 pregnancy outcomes in women with inflammatory bowel disease (IBD) to 384,811 women without bowel disease from a UK database, and reported a non-significant adjusted OR of 0.98 (95% CI 0.73, 1.31) for any major birth defect. (Boyd et al., 2015) using data from the Danish National Birth Cohort studied 644 pregnant women with IBD compared to 83,795 with no bowel disease. No increased risk for pregnancy loss, or risk for major birth defects overall, was noted. However, there was an approximate 2-fold increased risk for preterm delivery for any IBD.

In a UK study, 1,969 pregnant women with IBD were identified in 364,363 singleton pregnancies ending in live birth or stillbirth (Abdul Sultan et al., 2016). Women with UC were at increased risk of preterm birth (adjusted OR 1.33 95% CI, 1.0, 1.67). No statistical differences were identified for risk for stillbirth, preeclampsia, caesarian section, or low birth weight.

Auger et al. (2020) studied 13,099 women from Quebec, Canada with Crohn's Disease and 7,798 with UC to determine if IBD was associated with a risk for birth defects. No association with an overall risk birth defects for women with IBD compared to women without IBD was identified. Adjusted analysis identified an increase risk specifically in abdominal wall defects in women with IBD (1.70, 95% CI 1.07, 2.71) compared to women without IBD; however when stratifying by disease, this risk was not present with UC alone (1.31 95% CI 0.54, 3.14). UC was associated with a risk for central nervous system defects (1.53, 95% CI 1.02-2.30).

Mahadevan et al. (2021) in the U.S.-based PIANO Registry studied 1,490 completed pregnancies with IBD with exposure to various medications. These included biologics as a group consisting of exposure to infliximab, adalimumab, certolizumab pegol, vedolizumab, golimumab, natalizumab, and ustekinumab; and thiopurines including azathioprine and 6-mercaptopurine. None of the exposure groups were found to increase the rate of major birth defects, spontaneous abortions, preterm birth, low birth weight, or infections during the first year of life. However, higher disease activity itself was associated with an increased risk of spontaneous abortion (Hazard Ratio [HR] 3.41; 95% CI 1.51, 7.69). Preterm birth was associated with increased risk of infant infection (OR 1.73; 95% CI 1.19, 2.51).

Risks for Adverse Pregnancy Outcomes Associated with Maternal Exposure to Tofacitinib

Limited information has been published regarding exposure to tofacitinib during pregnancy, with the majority of data collected after exposure during clinical trials or post-marketing studies (Clowse et al, 2016; Mahadevan et al, 2018; Monfared et al, 2023). All reports indicated exposure took place in at least the first trimester.

Clowse et al (2016) reported on pregnancy outcomes of 47 women who became pregnant while in a tofacitinib randomized controlled trial through April 2014 for the treatment of RA or

psoriasis. Of the 47 pregnancies, 31 (66.0%) were treated for RA, and 16 (34.0%) were treated for psoriasis. Thirteen of the 31 pregnancies treated for RA received a combination of tofacitinib and methotrexate. The study reported 25 (53.2%) healthy newborns, 7 (14.9%) spontaneous abortions, 8 (17.0%) medical terminations, 1 (2.1%) with a major birth defect (tofacitinib without methotrexate), and 6 (12.8%) cases pending outcome or lost-to-follow-up. Clowse et al concluded that the outcomes were consistent with background risks in the general population and in patients with RA and psoriasis.

Mahadevan et al (2018) presented data collected up to March 2017 on 11 of 74 cases of exposure to tofacitinib during pregnancy in women enrolled in UC interventional studies, as well as updated data for RA and psoriasis previously reported by Clowse et al (2016). Of the 74 pregnancies exposed to tofacitinib for RA, PsA, psoriasis or UC, 37 (50.0%) were reported to be healthy newborns. There were 12 (16.2%) reports of spontaneous abortion, 13 (17.6%) medical termination, 11 (14.9%) pending outcome or lost-to-follow-up, and 1 (1.4%) report of a major birth defect (pulmonary valve stenosis). Mahadevan et al, reported that of the 11 cases exposed to tofacitinib for UC in the first trimester, 4 (36.3%) of the pregnancies resulted in healthy newborns, 2 (18.2%) in spontaneous abortions, 2 (18.2%) in medical terminations, and 3 (27.3%) cases were pending outcome or lost-to-follow-up. Of the 4 healthy outcomes, 1 case of preterm delivery was reported. Mahadevan et al, concluded that based on the limited data available, pregnancy outcomes in women exposed to tofacitinib during pregnancy for UC appeared to be similar to the outcomes in other tofacitinib clinical trials populations and the general population.

Fernandez-Sanchez et al (2021) reported a case of a woman who became pregnant while on tofacitinib for the treatment of PsA until 2 to 3 weeks post-conception. The patient delivered a healthy, preterm baby.

Monfared et al (2023) conducted a systematic review of literature on safety of novel small molecules in pregnancy. The authors reported that all data reviewed for tofacitinib exposure were included in the Pfizer Summary of Product Characteristics, 2023, with the exception of 4 cases reported by Vinet et al, 2019. There was a total of 126 pregnancies reported (including data from Clowse et al, 2016; Mahadevan et al, 2018, Fernandez-Sanchez et al, 2021. Of the 126 reported pregnancies, 55 (43.7%) were live born infants, 15 (11.9%) spontaneous abortions, 14 (11.1%) medical terminations, and 42 (33.3%) of outcomes were unknown or lost-to-follow-up. Two (1.6%) major birth defects were reported; one case with pulmonary valve stenosis (reported by Clowse et al, 2016), and one case with a ventricular septal defect. One serious infection was reported. Nineteen of the pregnancies were concomitantly exposed to methotrexate. Monfared et al (2023) concluded that overall data were not concerning, however data for novel small molecule use in pregnancy was considered limited.

Summary of Findings in the OTIS Tofacitinib Pregnancy Cohort Study

Although no formal comparisons were made, maternal characteristics of those in the tofacitinib-exposed cohort exhibited a nominally higher risk profile for adverse pregnancy outcomes than either of the comparison groups on several covariates. These included non-white race/ethnicity, lower educational attainment, lower household income, lower proportion taking prenatal vitamins/folic acid supplements at conception, higher RA/PsA disease severity/disability scores at enrollment, and higher proportion reporting comorbid depression and pre-existing hypertension.

For the primary outcome of major birth defects, there was one defect reported among eight pregnancies ending in at least one live birth (12.5%, 95% CI 0.66, 48.01) vs 3/88 (3.4%, 95% CI 0.91, 8.96) in the diseased unexposed cohort, and 8/92 (8.7%, 95% CI 4.16, 15.81) in the non-diseased unexposed comparison cohort. The reported major birth defect in the tofacitinib-exposed cohort was congenital chordee with first degree hypospadias. There was no pattern of minor anomalies identified in the small subset that received the dysmorphology examination.

The estimated rate of spontaneous abortion in the tofacitinib-exposed group was 28.3% with wide CIs and a lower bound of 4.6%; however, this estimate was based on one event. Similarly, the estimated rate of preterm delivery in the tofacitinib-exposed group was 23.5% with wide CIs and a lower bound of 6.5% but was based on only two events. There were no stillbirths reported in any cohort. The proportion of live born singletons small for gestational age on weight and head circumference exceeded the expected 10% based on two and one events, respectively. Similarly, the proportion of live born singleton infants small on postnatal growth in the tofacitinib-exposed group exceeded the expected 10% but was based on one event. There were no serious or opportunistic infections or malignancies reported in the tofacitinib cohort in the first year of life.

In summary, the rates of specific adverse pregnancy outcomes that were included in this study (e.g., major and minor birth defects, spontaneous abortion, stillbirth, preterm delivery, small for gestational age, postnatal growth, serious or opportunistic infections and malignancies) were based on extremely small numbers of events with very wide confidence intervals, and cannot be used to generalize to any risk or safety estimates for the population of tofacitinib-exposed pregnancies. However, taken in the context of the limited number of previous reports, these data do not suggest a signal for a pattern of adverse outcomes associated with tofacitinib exposure. This is further supported by the lack of a pattern of major structural defects and no pattern of minor structural anomalies.

Additional data provided in the Exposure Series (summarized in Annex 2 Additional Data, Appendix A.2., A.3., A.4) identified one infant with major birth defects (cleft palate (submucous), cleft larynx, congenital deviated nasal septum to the right with midnasal stenosis) that was not similar to the one reported in the prospective cohort, nor similar to previously reported defects. In addition, in the Exposure Series, another 4 infants received the dysmorphology examination and no pattern of minor defects was identified in that group as well.

11.1. Key Results

There were few adverse events reported this study among the 11 tofacitinib-exposed pregnancies that were enrolled in the cohort, including 1 major birth defect (relative to 3/88 in the disease-matched unexposed cohort and 8/92 in the non-diseased matched unexposed cohort), 1 spontaneous abortion (relative to 7/97 in the diseased-matched unexposed cohort and 1/97 in the non-diseased unexposed cohort), and 2 preterm deliveries (relative to 7/87 in the diseased-matched unexposed cohort and 4/93 in the non-diseased unexposed cohort). By definition, approximately 10% of infants are expected to meet the criteria for small for gestational age (SGA) at delivery due to the normal distribution of infant size. In the tofacitinib-exposed cohort, there were 2 infants SGA on weight, 1 SGA on head circumference, and 1 small for age on postnatal weight (percentages in the comparator cohorts were at or below the 10th centile for all three measures of SGA). There

were no stillbirths (and none in the comparator cohorts), no serious or opportunistic infections (relative to 7/90 in the diseased-matched unexposed cohort and 4/93 in the non-diseased unexposed cohort) and no malignancies reported in the first year of life (none also reported in the comparator cohorts). Overall, the sample size for the tofacitinib-exposed cohort was extremely limited. However, based on this limited sample size, there was no pattern of major or minor anomalies identified.

11.2. Limitations

This study had several limitations. The primary limitation was sample size in the exposed cohort. While extensive data was collected on potential confounders, the limited sample size prevented any comparative adjusted analyses to address confounding. Additionally, the study approach was prospective but not randomized. The study relied on volunteers which could have led to selection bias. Sources of bias in this study are further outlined in Section 9.6.

11.3. Interpretation

Due to the small sample size of tofacitinib-exposed pregnancies in this study, the findings are limited in interpretability. However, consistent with previously published, but also limited data, there was no evidence of a pattern of major birth defects, and, in this study, no evidence of a pattern of minor structural birth defects. There were no stillbirths, serious or opportunistic infections, or malignancies reported.

11.4. Generalizability

The sample size was too limited to support generalization to tofacitinib exposed pregnancies.

12. OTHER INFORMATION

Not Applicable

13. CONCLUSIONS

Based on very small numbers in this prospective safety study, there was no evidence of a pattern of major or minor structural birth defects in the tofacitinib-exposed cohort. There were also no stillbirths, and among live born infants, there were no serious or opportunistic infections, or malignancies reported in the first year of life.

The animal data have raised concerns for use of the medication during pregnancy. Data presented for this project are too limited to draw definitive conclusions.

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15. LIST OF SOURCE TABLES AND FIGURES

Not Applicable

ANNEX 1 LIST OF STAND ALONE DOCUMENTS

1. Abstract
2. Signatures
3. Protocol
4. SAP
5. Telemedicine Dysmorphology Exam Form

ANNEX 2 ADDITIONAL DATA

Appendix A.2 Tofacitinib Exposure Series

A total of 24 pregnancies with tofacitinib exposure did not meet the criteria for enrollment in the cohort (Sections 9.3.2 and 9.3.3). The reason for exclusion from the cohort are presented in Annex 2, Table 33. The data on maternal characteristics and for each outcome are presented for those in the exposure series group who were prospectively enrolled separately from those who were retrospectively enrolled, as well as combined.

The overall findings are summarized in Table 19 to Table 29. One infant with major birth defects was reported in the prospective exposure series group. This translated to 1/16 (6.2%, 95% CI 0.36, 27.16) in pregnancies ending in at least one live born infant, and 1/23 (4.3%, 95% CI 0.26, 19.61) in all pregnancies excluding lost-to follow-up (Table 21). The infant with the major birth defect had submucous cleft palate, cleft larynx, and congenital deviated nasal septum to the right with midnasal stenosis (Annex 2, Table 32). Four infants received the dysmorphology examination in the prospective exposure series, and none had a pattern of malformation (Table 23).

Spontaneous abortion occurred in 0/12 pregnancies in the prospective exposure series group (Table 24). Preterm delivery occurred in 2/16 pregnancies in the prospective exposure series group, for an estimated rate of 12.1% (95% CI 3.2%, 40.4%) (Table 25). The prospectively enrolled exposure series group had a higher proportion of infants than the expected 10% in the general population that were small for gestational age on head circumference at birth (37.5%, 95% CI 16.86, 62.32). However, the proportions were within the expected range of 10% in the general population small for age on head circumference at the one-year follow-up time-point (Table 26 and Table 27). Serious or opportunistic infections were identified in 3/16 infants up to one-year of age in the prospective exposure group (18.8%, 95% CI 6.17, 44.75) (Table 28). No malignancies were reported in any infant up to one year of age.

Table 19. Maternal Characteristics of Pregnancies Exposed to Tofacitinib (Exposure Series)

	Tofacitinib Prospective Exposure Series (N = 18) n (%)	Tofacitinib Retrospective Exposure Series (N = 6) n (%)	Tofacitinib Exposure Series Total (N = 24) n (%)
Maternal Demographics			
Maternal age (years) at estimated delivery date, categorical, n (%) <25 years 25-29 years 30-34 years >34 years	 0 3 (16.7) 8 (44.4) 7 (38.9)	 0 0 3 (50.0) 3 (50.0)	 0 3 (12.5) 11 (45.8) 10 (41.7)
Maternal Age at Estimated Due Date - Mean (Standard Deviation)	33.6 (3.9)	36.4 (5.4)	34.3 (4.4)
Maternal race, n (%) White Black Asian/Pacific Islander Native American Other	 13 (72.1) 1 (5.6) 0 3 (16.7) 1 (5.6)	 4 (66.6) 1 (16.7) 0 0 1 (16.7)	 17 (70.8) 2 (8.3) 0 3 (12.5) 2 (8.3)
Maternal ethnicity, n (%) Non-Hispanic Hispanic	 17 (94.4) 1 (5.6)	 5 (83.3) 1 (16.7)	 22 (91.7) 2 (8.3)
Maternal education category, n (%) <12 years 12-15 years >15 years	 0 5 (27.8) 13 (72.2)	 0 1 (16.7) 5 (83.3)	 0 6 (25.0) 18 (75.0)
Hollingshead socioeconomic category[a], n (%) Low (4 or 5) Medium to High (1, 2, or 3)	 1 (5.6) 17 (94.4)	 0 6 (100.0)	 1 (4.2) 23 (95.8)
Maternal Height (cm) -Mean (Standard Deviation)	166.1 (6.1)	170.6 (10.2)	167.2 (7.4)
Maternal Pre-pregnancy Body Weight (kg) - Mean (Standard Deviation)	71.7 (12.2)	82.7 (21.0)	74.4 (15.2)
Maternal pre-pregnancy body mass index (BMI), n (%) <18.5 (underweight) 18.5-<25 (normal weight) 25-<30 (overweight) ≥30 (obese)	 0 9 (50.0) 7 (38.9) 2 (11.1)	 0 2 (33.3) 3 (50.0) 1 (16.7)	 0 11 (45.8) 10 (41.7) 3 (12.5)
Gestational Age at Time of Enrollment – Weeks - Mean (Standard Deviation)	15.9 (9.0)	21.0 (13.5)	17.2 (10.2)

Table 19. Maternal Characteristics of Pregnancies Exposed to Tofacitinib (Exposure Series)

	Tofacitinib Prospective Exposure Series (N = 18) n (%)	Tofacitinib Retrospective Exposure Series (N = 6) n (%)	Tofacitinib Exposure Series Total (N = 24) n (%)
Gestational Age at Time of Enrollment Category – Weeks, n (%)			
≤13 weeks	9 (50.0)	3 (50.0)	12 (50.0)
>13 - <20 weeks	3 (16.7)	1 (16.7)	4 (16.7)
≥20 weeks	6 (33.3)	2 (33.3)	8 (33.3)
Referral source, n (%)			
Sponsor	1 (5.6)	0	1 (4.2)
Health-care Professional	11 (61.1)	4 (66.6)	15 (62.5)
Internet	2 (11.1)	0	2 (8.3)
OTIS Member Service	1 (5.6)	1 (16.7)	2 (8.3)
Other	3 (16.6)	1 (16.7)	4 (16.7)
Country of residence, n (%)			
U.S.	18 (100.0)	6 (100.0)	24 (100.0)
Canada	0	0	0
Family Income Category, n (%)			
<$10,000	0	0	0
$10,000 - <$50,000	3 (16.7)	0	3 (12.5)
≥$50,000	15 (83.3)	6 (100.0)	21 (87.5)
Year of Enrollment, n (%)			
Years 2010-2014	1 (5.6)	0	1 (4.2)
Years 2015-2018	10 (55.6)	4 (66.7)	14 (58.3)
Years 2019-2023	7 (38.8)	2 (33.3)	9 (37.5)
Intended Pregnancy, n (%)	10 (55.6)	3 (50.0)	13 (54.2)
In Vitro Fertilization (IVF), n (%)	0	0	0
Paternal Demographics			
Paternal age (years) at estimated delivery date, categorical[b], n (%)			
<25 years	0	0	0
25-29 years	4 (23.5)	0	4 (17.4)
30-34 years	3 (17.6)	3 (50.0)	6 (26.1)
>34 years	10 (58.8)	3 (50.0)	13 (56.5)
Paternal Age at Estimated Due Date - Mean (Standard Deviation)	34.6 (5.7)	37.4 (5.5)	35.4 (5.7)
Pregnancy History			

Table 19. Maternal Characteristics of Pregnancies Exposed to Tofacitinib (Exposure Series)

	Tofacitinib Prospective Exposure Series (N = 18) n (%)	Tofacitinib Retrospective Exposure Series (N = 6) n (%)	Tofacitinib Exposure Series Total (N = 24) n (%)
Gravidity – Number of times ever pregnant, n (%)			
1	5 (27.8)	2 (33.3)	7 (29.2)
2-3	9 (50.0)	2 (33.3)	11 (45.8)
4-5	3 (16.7)	2 (33.3)	5 (20.8)
≥6	1 (5.5)	0	1 (4.2)
Parity – Number of previous live birth or stillbirth deliveries, n (%)			
0	8 (44.4)	3 (50.0)	11 (45.8)
1-2	9 (50.0)	2 (33.3)	11 (45.8)
3-4	1 (5.6)	1 (16.7)	2 (8.3)
≥5	0	0	0
Number of previous pregnancies ending in spontaneous abortion[c], n (%)			
0	13 (72.2)	4 (66.7)	17 (70.8)
1	3 (16.7)	2 (33.3)	5 (20.8)
2	2 (11.1)	0	2 (8.3)
≥3	0	0	0
Number of previous pregnancies ending in elective termination/abortion, n (%)			
0	15 (83.3)	5 (83.3)	20 (83.3)
1	2 (11.1)	1 (16.7)	3 (12.5)
2	1 (5.6)	0	1 (4.2)
≥3	0	0	0
Previous pregnancies with a major birth defect, n (%)	1 (5.6)	0	1 (4.2)
Previous pregnancies ending in preterm delivery, n (%)	3 (16.7)	0	3 (12.5)
Number of times enrolled, n(%)			
1	16 (88.8)	5 (83.3)	21 (87.5)
2	1 (5.6)	1 (16.7)	2 (8.3)
3	1 (5.6)	0	1 (4.2)
4	0	0	0
Maternal Disease			
Years Since Diagnosis of Primary Disease – Year – Mean (Standard Deviation)	9.1 (9.2)	7.3 (1.7)	8.7 (8.0)

Table 19. Maternal Characteristics of Pregnancies Exposed to Tofacitinib (Exposure Series)

	Tofacitinib Prospective Exposure Series (N = 18) n (%)	Tofacitinib Retrospective Exposure Series (N = 6) n (%)	Tofacitinib Exposure Series Total (N = 24) n (%)
Maternal Age at Diagnosis of Primary Disease – Year – Mean (Standard Deviation)	24.2 (10.3)	30.6 (4.1)	25.8 (9.5)
RA Disease Severity Score			
Intake - Rheumatic 1[d]- Mean (Standard Deviation)	0.6 (0.6)	----	0.6 (0.6)
Intake - Rheumatic 2[e]- Mean (Standard Deviation)	38.8 (29.2)	----	38.8 (29.2)
Intake - Rheumatic 3[f]- Mean (Standard Deviation)	34.0 (23.4)	----	34.0 (23.4)
2nd Trimester (20 week) - Rheumatic 1[d]- Mean (Standard Deviation)	0.3 (0.4)	----	0.3 (0.4)
2nd Trimester (20 week) - Rheumatic 2[e]- Mean (Standard Deviation)	35.0 (19.4)	----	35.0 (19.4)
2nd Trimester (20 week) - Rheumatic 3[f]- Mean (Standard Deviation)	27.9 (17.3)	----	27.9 (17.3)
3rd Trimester (32 week) - Rheumatic 1[d]- Mean (Standard Deviation)	0.6 (0.8)	----	0.6 (0.8)
3rd Trimester (32 week) - Rheumatic 2[e] – Mean (Standard Deviation)	39.2 (27.7)	----	39.2 (27.7)
3rd Trimester (32 week) - Rheumatic 3[f]– Mean (Standard Deviation)	34.2 (23.7)	----	34.2 (23.7)
UC Disease Severity Score			
Intake – UC[g,h] – Mean (Standard Deviation)	5.7 (0.7)	----	5.7 (0.7)
2nd Trimester (20 week) – UC[g,i] - Mean (Standard Deviation)	5.6 (1.0)	----	5.6 (1.0)
3rd Trimester (32 week) – UC[g,j] - Mean (Standard Deviation)	6.4 (0.3)	----	6.4 (0.3)
Maternal Exposure			
Prenatal, multivitamin or folic acid supplement use and timing in pregnancy, n (%) Began prior to conception Post-conception only Have not taken at all	8 (44.4) 10 (55.6) 0	6 (100.0) 0 0	14 (58.3) 10 (41.7) 0
Any alcohol use in pregnancy, n (%)	7 (38.9)	2 (33.3)	9 (37.5)
Any tobacco use in pregnancy, n (%)	1 (5.6)	0	1 (4.2)
Any caffeine use in pregnancy, n (%)	15 (83.3)	3 (50.0)	18 (75.0)

Table 19. Maternal Characteristics of Pregnancies Exposed to Tofacitinib (Exposure Series)

	Tofacitinib Prospective Exposure Series (N = 18) n (%)	Tofacitinib Retrospective Exposure Series (N = 6) n (%)	Tofacitinib Exposure Series Total (N = 24) n (%)
Prednisone and/or Systemic Oral Corticosteroid, n (%)	8 (44.4)	2 (33.3)	10 (41.7)
Methotrexate Use in Pregnancy - n (%)	0	0	0
Exposure to a Known Human Teratogen in Pregnancy, n (%)	0	0	0
Dose and Frequency of Tofacitinib			
10 mg per day	12 (66.7)	1 (16.7)	13 (54.2)
5 mg per day	0	1 (16.7)	1 (4.2)
Other[k]	6 (33.3)	4 (66.6)	10 (41.6)
Gestational Timing of Tofacitinib Dose in Pregnancy, n(%)			
Exposure Prior to LMP only	0	0	0
LMP to < DOC only[m]	0	0	0
1st Trimester only	10 (58.8)	6 (100.0)	16 (69.6)
1st and 2nd Trimesters only	0	0	0
1st and 3rd Trimesters only	0	0	0
1st, 2nd, and 3rd Trimesters	7 (41.2)	0	7 (30.4)
2nd Trimester only	0	0	0
2nd and 3rd Trimesters only	0	0	0
3rd Trimester only	0	0	0
Prenatal Diagnostic Tests Performed Prior to Enrollment, n (%)			
Ultrasound Level 1	15 (83.3)	5 (83.3)	20 (83.3)
Ultrasound Level 2	6 (33.3)	0	6 (25.0)
Chorionic villus sampling (CVS)	0	0	0
Amniocentesis	0	0	0
Prenatal Diagnostic Tests Performed Anytime in Pregnancy, n (%)			
Ultrasound Level 1	18 (100.0)	5 (83.3)	23 (95.8)
Ultrasound Level 2	18 (100.0)	0	18 (75.0)
Chorionic villus sampling (CVS)	0	0	0
Amniocentesis	1 (5.6)	0	1 (4.2)
Maternal Comorbidity, n (%)			

Table 19. Maternal Characteristics of Pregnancies Exposed to Tofacitinib (Exposure Series)

	Tofacitinib Prospective Exposure Series (N = 18) n (%)	Tofacitinib Retrospective Exposure Series (N = 6) n (%)	Tofacitinib Exposure Series Total (N = 24) n (%)
Ankylosing Spondylitis	1 (5.6)	0	1 (4.2)
Asthma	6 (33.3)	0	6 (25.0)
Autoimmune Disease, Other	2 (11.1)	0	2 (8.3)
Crohn's Disease	1 (5.6)	1 (16.7)	2 (8.3)
Depression	7 (38.9)	2 (33.3)	9 (37.5)
Chronic Hypertension	0	1 (16.7)	1 (4.2)
Lupus	0	0	0
Multiple Sclerosis	0	0	0
Psoriasis	1 (5.6)	0	1 (4.2)
Psychiatric Condition	0	0	0
Thyroid Dysfunction	0	0	0

N: Number of participants with outcome.

a. Based on four-factor Hollingshead categories incorporating maternal and paternal education and occupation; highest socioeconomic status category = 1; lowest socioeconomic status category = 5.
b. Participants with paternal age at birth missing- Case Series Prospective group: 1
c. Includes molar pregnancies, blighted ovum, and ectopic pregnancies.
d. RA 1: Maternal report of disease severity score expressed as the HAQ-DI summary score; possible score ranges from 0-3 with higher score representing higher severity/disability
e. RA 2: Maternal report of experience of disease-related pain; possible score 0-100 with higher score indicating more pain
f. RA 3: Maternal report of how overall illness affects her; possible score 0-100 with higher score indicating more effect
g. SBDIQ: Short IBD Questionnaire, an instrument to measure quality of life in participants with IBD (CD/UC); possible score 0-7 with lower score indicating poor quality of life.
h. Participants with Intake UC score missing- Case Series Retrospective group: 6
i. Participants with Intake UC score missing- Case Series Prospective group: 15, Case Series Retrospective group: 6
j. Participants with Intake UC score missing- Case Series Prospective group: 14, Case Series Retrospective group: 6
k. Other doses: Six participants took 11 mg per day, two participants took 10 mg two times per day, one participant took 5 mg three times per day, one participant took 20 mg once per day.
l. Participants with gestational timing of Tofacitinib in pregnancy missing- Case Series Prospective group: 1
m. Standard definition of the 1st trimester is [0, 11] weeks' post conception, the 2nd trimester is (11, 24] weeks' post conception, the 3rd trimester is (24, 43] weeks' post conception. In this table, the 1st trimester includes last menstrual period (LMP) to date of conception (DOC), i.e. if a participant is exposed in both LMP to DOC and the 1st trimester, she will be in the category of '1st Trimester'"

Table 20. Pregnancy Outcome in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series (N = 18) n/N' (%)	Tofacitinib Retrospective Exposure Series (N = 6) n/N' (%)	Tofacitinib Exposure Series Total (N = 24) n/N' (%)
Live birth	16/18 (88.9)	0/6 (0.0)	16/24 (66.7)
Twin	0/16 (0.0)	----	0/16 (0.0)
Twin with like sex	----	----	----
Sex (male)	----	----	----
Twin with non like sex	----	----	----
Twin with only one surviving	----	----	----
Sex (male)	----	----	----
Singleton	16/16 (100.0)	----	16/16 (100.0)
Sex (male)	12/16 (75.0)	----	12/16 (75.0)
Caesarian	7/16 (43.8)	----	7/16 (43.8)
Spontaneous Abortion[a]	0/18	6/6	6/24
Spontaneous Abortion-Twins	----	1/6	1/6
Stillbirth	1/18 (5.6)	0/6 (0.0)	1/24 (4.2)
Termination	0/18 (0.0)	0/6 (0.0)	0/24 (0.0)
Social	----	----	----
Medical	----	----	----
Lost to Follow Up	1/18 (5.6)	0/6 (0.0)	1/24 (4.2)
No Contact	1/1 (100.0)	----	1/1 (100.0)
Withdrew	0/1 (0.0)	----	0/1 (0.0)

[a]Left Truncation Accounted Spontaneous Abortion Rate in Table 24
N: Number of participants with pregnancy outcome
n/N' (%) is either out of total N or % of the N' subcategories under the live birth, spontaneous abortion, stillbirth, termination or lost to follow-up rows.

Table 21. Major Birth Defects in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series n/N (%)	Tofacitinib Retrospective Exposure Series n/N (%)	Tofacitinib Exposure Series Total n/N (%)
Number of pregnancies ending with at least one live born infant with a major birth defect	1/16 (6.2) [0.36, 27.16]	----	1/16 (6.2) [0.36, 27.16]
Number of all pregnancies (excluding lost-to-follow-up) with major birth defects	1/17 (5.9) [0.31, 25.71]	0/6 (0.0) [0.00, 39.30]	1/23 (4.3) [0.26,19.61]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

Table 22. Major Birth Defects among Pregnancies with Multiple Births in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series n/N (%)	Tofacitinib Retrospective Exposure Series n/N (%)	Tofacitinib Exposure Series Total n/N (%)
Number of pregnancies ending with at least one live born infant with a major birth defect	----	----	----
Number of all pregnancies (excluding lost-to-follow-up) with major birth defects	----	0/1 (0.0) [0.00, 95.00]	0/1 (0.0) [0.00, 95.00]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

Table 23. Number of Infants with Three or More or a Pattern of Minor Malformations among All Infants Receiving the Dysmorphological Examination[a] in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series n/N (%)	Tofacitinib Retrospective Exposure Series n/N (%)	Tofacitinib Exposure Series Total n/N (%)
Number of infants who received the Exam/Number of infants eligible for Exam	4/16 (25.0) [9.71, 50.82]	----	4/16 (25.0) [9.71, 50.82]
Number of infants examined with at least 3 or more of any minor malformations[b]	2/4 (50.0) [12.35, 87.65]	----	2/4 (50.0) [12.35, 87.65]
Number of infants examined with a pattern of 3 or more minor malformations[c]	0/4 (0.0) [0.00, 0.00]	----	0/4 (0.0) [0.00, 0.00]

[a]95% CI estimated using the generalized estimating equations (GEE) approach, logit--binomial link and independent working correlation.
[b]Includes singletons and multiples who received the dysmorphological exam
[c]Includes singletons and multiples who received the dysmorphological exam for consideration of pattern; however, co-twins with the same three or more minor structural defects could not constitute a pattern on their own

Table 24. Spontaneous Abortion (SAB) among Women Prospectively Enrolled and Exposed prior to 20 Weeks' Gestation and with Follow Up in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series (N = 12)
Number of SAB Events[a]	0
Left Truncation Accounted SAB Rate[b,c]	0.0%

[a]In pregnancies involving multiples (twins/triplets) with one or more of the outcomes ending in spontaneous abortion, when there are no live births, the pregnancy is counted as one spontaneous abortion event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.
[b]SAB rate computed using Fleming-Harrington estimate at 20 weeks' gestation, accounting for left truncation because women can enroll at various times in gestation.
[c]Earliest gestational age at enrollment (weeks): Prospective 3.0
N: Number of participants enrolled and exposed prior to 20 weeks' gestation and with follow up.

Table 25. Preterm Delivery (PTD) among Pregnancies Prospectively Enrolled and Exposed prior to 37 Weeks Gestation and Ending in Live Birth or LTFU with at Least One Day Follow-up (Multiple Births Excluded) in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series (N = 16)
Number of PTD (n)[a]	2
Left Truncation Accounted PTD Rate[b]	12.1% [3.2%, 40.4%]

[a]Computed using Fleming-Harrington estimate at 37 weeks gestation, accounting for left truncation due to varying time in gestation at enrollment.
[b]One case was excluded due to having zero days of follow-up.
N: Number of participants enrolled and exposed prior to 37 weeks' gestation, ending in live birth singleton or LTFU with at least one day follow-up.

Table 26. Small for Gestational Age (SGA) at Birth Among Live Born Infants (Multiple Pregnancies Excluded)[a] in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series (N = 16) n/N' (%)	Tofacitinib Retrospective Exposure Series (N = 0) n/N' (%)	Tofacitinib Exposure Series Total (N = 16) n/N' (%)
SGA on Weight	0/16 (0.0) [0.00, 17.07]	----	0/16 (0.0) [0.00, 17.07]
SGA on Length	0/16 (0.0) [0.00, 17.07]	----	0/16 (0.0) [0.00, 17.07]
SGA on Occipitofrontal Circumference (OFC)	6/16 (37.5) [16.86, 62.31]	----	6/16 (37.5) [16.86, 62.31]
SGA on weight and/or length, but not OFC	0/16 (0.0) [0.00, 17.07]	----	0/16 (0.0) [0.00, 17.07]
SGA on weight and/or length, and OFC	0/16 (0.0) [0.00, 17.07]	----	0/16 (0.0) [0.00, 17.07]

[a]SGA defined as ≤10th centile for gestational age and sex.
N: Number of singleton live born infants.
N' at each category of growth measurement: Number of live born singletons for whom the specific growth measurement is available.

Table 27. Postnatal Growth at Approximately One Year - Percentile ≤10th (Multiple Births Excluded) in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series (N = 16) n/N' (%)	Tofacitinib Retrospective Exposure Series (N = 0) n/N' (%)	Tofacitinib Exposure Series Total (N = 16) n/N' (%)
Weight ≤10th centile[a]	1/11 (9.1) [0.46, 37.31]	----	1/11 (9.1) [0.46, 37.31]
Length ≤10th centile[a]	0/11 (0.0) [0.00, 17.07]	----	0/11 (0.0) [0.00, 17.07]
Occipitofrontal Circumference ≤10th centile[a]	1/11 (9.1) [0.46, 37.31]	----	1/11 (9.1) [0.46, 37.31]

[a]≤10th centile for chronological age. Age adjusted if child is less than 12 months, unadjusted if ≥12 months. Measurements are taken at 12 months of age +/- 3 months
N: Number of singleton infants who have reached one year of age
% = (n/N') * 100: N' at each category of growth measurement: Number of singleton infants for whom the specific percentile information is available.

Table 28. Postnatal Events - Serious and Opportunistic Infections in Infants up to One Year of Age (Including Infants from Multiple Births) in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series (N = 16) n/N' (%)	Tofacitinib Retrospective Exposure Series (N = 0) n/N' (%)	Tofacitinib Exposure Series Total (N = 16) n/N' (%)
Serious or Opportunistic Infections in Infants up to One Year of Age (Including Infants from Multiple Births)	3/16 (18.8) [6.17, 44.75]	----	3/16 (18.8) [6.17, 44.75]

95% CI estimated using the generalized estimating equations (GEE) approach, logit--binomial link and independent working correlation.
N: Number of live born infants.
% = (n/N) * 100; N': Number of live born infants with the event yes/no and event timing information available.

Table 29. Postnatal Events - Malignancies in Infants up to One Year of Age (Including infants from Multiple Births) in Tofacitinib Exposure Series

	Tofacitinib Prospective Exposure Series (N = 16) n/N' (%)	Tofacitinib Retrospective Exposure Series (N = 0) n/N' (%)	Tofacitinib Exposure Series Total (N = 16) n/N' (%)
Malignancies in Infants up to One Year of Age (Including Infants from Multiple Births)	0/16 (0.0) [0.00, 0.00]	----	0/16 (0.0) [0.00, 0.00]

95% CI estimated using the generalized estimating equations (GEE) approach, logit--binomial link and independent working correlation.
N: Number of live born infants.
% = (n/N) * 100; N': Number of live born infants with the event yes/no and event timing information available.

Appendix A.3 Tofacitinib-Exposed Cohort and Prospective Exposure Series Combined Major Birth Defect Analysis

Below the analyses for the primary outcome of major birth defects combining the tofacitinib-exposed cohort and tofacitinib-exposed prospective exposure series outcomes are presented (Table 30 and Table 31). The combined rate of major birth defects among pregnancies ending in at least one live birth was 2/24 (8.3%, 95% CI 1.46, 24.86). When including all pregnancies, excluding lost-to-follow-up, the result was 2/26 (7.7%, 95% CI 1.36, 23.16). There were no tofacitinib-exposed pregnancies with co-exposure to a known human teratogen or defects that were thought to be of chromosomal or genetic origin, so sensitivity analyses excluding these participants were not performed.

Table 30. Birth Defects Among Pregnancies in the Tofacitinib Exposed Cohort and Prospective Exposure Series

	Tofacitinib Exposed Cohort and Exposure Series Prospective n/N (%)
Number of pregnancies ending with at least one live born infant with a major birth defect	2/24 (8.3) [1.46, 24.86]
Number of all pregnancies (excluding lost-to follow-up) with major birth defects	2/26 (7.7) [1.36, 23.16]

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

Table 31. Major Birth Defects Among Pregnancies with Multiple Births in the Tofacitinib Exposed Cohort and Prospective Exposure Series

	Tofacitinib Exposed Cohort and Exposure Series Prospective n/N (%)
Number of pregnancies ending with at least one live born infant with a major birth defect	----
Number of all pregnancies (excluding lost-to follow-up) with major birth defects	----

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

Annex 2

Appendix A.4 Major Structural Birth Defects Line-Listing for all Cohort Groups and Exposure Series

Table 32. Major Structural Birth Defects Line-Listing for all Cohort Groups and Exposure Series

Group	Birth Defects
Tofacitinib-Exposed Cohort	1. Congenital chordee with first degree hypospadias, Pelviectasis[b], and Congenital hydronephrosis[b] (UC)
Disease-Matched Unexposed Comparison Cohort	1. Unspecified chromosomal anomalies (spontaneous abortion) (RA) 2. Pre-axial polydactyly (RA) 3. Patent ductus arteriosus (PDA), Cardiac arrhythmias[b] (UC) 4. Postaxial polydactyly, Type B (UC)
Non-Disease Unexposed Comparison Cohort	1. Microcephaly 2. Microcephaly 3. Trisomy 21 (Down syndrome) 4. Jacobsen syndrome, Duplication of chromosomes (11p14.3)[a], Persistent left superior vena cava, Congenital chordee without hypospadias, Inguinal hernia 5. Congenital chordee with first degree hypospadias 6. Patent foramen ovale (PFO) 7. Atrial septal defect (ASD), Pulmonary artery stenosis, Multiple hemangiomas 8. Multiple hemangiomas 9. Multiple hemangiomas
Tofacitinib Exposure Series	1. Cleft palate (submucous), Cleft larynx, Congenital deviated nasal septum to the right with midnasal stenosis (JIA)

[a] Not classified as a major structural birth defect
[b] Counted as a “functional” defect per the study and not classified as a major birth defect

Annex 2

Appendix A.5

Table 33. Reasons for Exclusions From the Tofacitinib Exposed Cohort

	Tofacitinib Exposure Series (N=24) n/N'(%)
Reasons for exclusion from the cohort[a]:	
Prospective Cases with Gestational Age at Enrollment ⩾20 Weeks	6/24 (25.0)
Post 1st Trimester Exposure	0/24 (0.0)
Preconception Exposure (last dose between LMP and conception)	0/24 (0.0)
Prenatal Diagnosis of a Major Malformation prior to Enrollment	0/24 (0.0)
Retrospective	6/24 (25.0)
Exclusionary Medication	4/24 (16.7)
Previous Enrollment in the Cohort	0/24 (0.0)
Not Diagnosed with the Study Related Diseases	14/24 (58.3)

[a]Participants may be counted more than once if they have more than one reason for being excluded from the cohort
N: Number of subjects enrolled in the registry group.
N': Number of subjects enrolled in the registry group and with information available.

Annex 2

Appendix A.6

Table 34. Line Listing of Participants in Tofacitinib-Exposed Cohort

Maternal Characteris-tics	Participant #1 16043	Participant #2 89660	Participant #3 91523	Participant #4 99087	Participant #5 104006	Participant #6 105192	Participant #7 115207	Participant #8 131828	Participant #9 132031	Participant #10 137248	Participant #11 143058
Year of cohort enrollment	2014	2018	2019	2019	2019	2020	2020	2021	2021	2021	2022
Specific autoimmune condition diagnosis	RA	RA	RA	UC	UC	UC	UC	RA	UC	UC	UC
Age at diagnosis of autoimmune condition	23	32	27	23	15	23	21	32	26	11	34
Year tofacitinib initiated	2013	2018	2018	2019	2019	2019	2018	2020	2019	2020	2019
Maternal age (years) at estimated delivery date	35	40	33	27	29	26	25	35	30	31	37
Maternal BMI	24.5	24.1	Unknown	22.7	28.3	21.3	29.2	24.2	46.4	34.9	25.8
Maternal use of alcohol during	Yes	No	No	No	Yes	No	No	No	No	No	No

Table 34. Line Listing of Participants in Tofacitinib-Exposed Cohort

Maternal Characteris-tics	Participant #1 16043	Participant #2 89660	Participant #3 91523	Participant #4 99087	Participant #5 104006	Participant #6 105192	Participant #7 115207	Participant #8 131828	Participant #9 132031	Participant #10 137248	Participant #11 143058
pregnancy (yes/no)											
Maternal use of tobacco during pregnancy (yes/no)	No	No	No	No	No	No	No	No	No	No	No
Maternal use of prenatal vitamins (including folic acid) yes/no	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Maternal use of concomitant medications (type and trimester of use)	Ambien (1st), Celebrex (1st), Lovenox (1st), Plaquenil (1st), Prednisone (1st, 2nd, 3rd), Zofran (1st, 2nd), Zyrtec (1st), Baby aspirin (1st, 2nd, 3rd), Miralax (1st, 2nd, 3rd), Tylenol (1st, 2nd, 3rd).	Levocetiri-zine dihydrochloride (1st)	Atenolol (1st), Atorvastatin (1st), Tylenol (1st)	Zofran (2nd), Tylenol (1st, 2nd), Rhogam (2nd)	Balsalazide disodium (1st, 2nd, 3rd), Heparin (3rd), Lovenox (1st, 2nd, 3rd), Prednisone (1st, 2nd, 3rd), Protonix (3rd), Sodium chloride (1st), Venofer (1st, 2nd,	Simvastatin (1st), Omeprazole (1st, 2nd, 3rd), Tums (1st, 2nd), Tylenol (1st, 2nd), Unisom (1st, 2nd)	Famotidine (1st, 2nd, 3rd), Prednisone (1st, 2nd, 3rd), Synthroid (1st, 2nd, 3rd), Zofran (1st), Tums (2nd, 3rd), Tylenol (1st, 2nd)	THC (1st, 2nd), Albuterol (1st, 2nd), Buspar (1st, 2nd), Gabapentin (1st, 2nd), Levothyroxine (1st, 2nd), Omeprazole (1st, 2nd), Singulair (1st, 2nd), Wellbutrin (1st, 2nd), Acetaminophen (1st, 2nd),	Advair (1st, 2nd, 3rd), Clomid (1st), Letrozole (1st), Mesalamine (1st, 2nd, 3rd), Metformin (1st, 2nd, 3rd), Pantoprazole (1st, 2nd, 3rd), Progesterone (1st), Zenpep (1st, 2nd, 3rd), Dayquil	Sertraline (1st, 2nd, 3rd), Lactase (1st, 2nd, 3rd), Tums (2nd, 3rd)	Balsalazide disodium (1st, 2nd, 3rd), Rhogam (3rd), Baby aspirin (2nd, 3rd), Zyrtec (1st, 2nd, 3rd)

Table 34. Line Listing of Participants in Tofacitinib-Exposed Cohort

Maternal Characteris -tics	Participant #1 16043	Participant #2 89660	Participant #3 91523	Participant #4 99087	Participant #5 104006	Participant #6 105192	Participant #7 115207	Participant #8 131828	Participant #9 132031	Participant #10 137248	Participant #11 143058
	Occupational exposure to x-rays (1st)				3rd), Tylenol (1st, 2nd)			Allegra (1st, 2nd)	(3rd), Robitussin (3rd), Sudafed (3rd), Tylenol (2nd, 3rd), Zyrtec (1st, 2nd, 3rd)		
Maternal use possible teratogens 3 months prior to cohort entry/enrollment (yes/no; if yes, type)	No	No	No	No	No	No	No	No	No	No	No
Paternal use of known teratogens (yes/no; if yes, type)	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Maternal comorbidities (including any infections during pregnancy) yes/no; if yes, type	No	Sjogren's, Uterine fibroids, Raynaud's, Depression	Ovarian cysts, Hypertension, High cholesterol	Marginal cord insertion (current pregnancy)	Anemia, MTHFR mutation, History of pulmonary embolism and renal vein thrombosis, History of blood	High cholesterol	Chronic gastritis, History of blood transfusions, Hypothyroidism, Anemia,	Fibromyalgia, Depression, Asthma, Hypothyroidism, Anxiety	COVID-19, MTHFR, Infertility, Asthma, PCOS	Depression, Anxiety, History of blood transfusions. Single umbilical artery	COVID-19

Table 34. Line Listing of Participants in Tofacitinib-Exposed Cohort

Maternal Characteris -tics	Participant #1 16043	Participant #2 89660	Participant #3 91523	Participant #4 99087	Participant #5 104006	Participant #6 105192	Participant #7 115207	Participant #8 131828	Participant #9 132031	Participant #10 137248	Participant #11 143058
					transfusions. Marginal cord insertion (current pregnancy)					(current pregnancy)	
Number of times ever pregnant	4	5	6	2	1	2	2	2	1	3	1
Number of previous livebirths	0	2	5	1	0	1	1	0	0	1	0
Number/ type of previous livebirths with major birth defect	0	0	0	0	0	0	1	0	0	0	0
Number/ type of previous livebirths with minor birth defects	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown
Maternal family history of major or minor birth	None reported	None reported	None reported	None reported	None reported	None reported	None reported	None reported	Aunt with cleft lip	None reported	None reported

Table 34. Line Listing of Participants in Tofacitinib-Exposed Cohort

Maternal Characteris-tics	Participant #1 16043	Participant #2 89660	Participant #3 91523	Participant #4 99087	Participant #5 104006	Participant #6 105192	Participant #7 115207	Participant #8 131828	Participant #9 132031	Participant #10 137248	Participant #11 143058
defects (yes/no)											
Paternal family history of major or minor birth defects (yes/no)	None reported	None reported	None reported	None reported	None reported	None reported	None reported	None reported	None reported	None reported	None reported
Number of previous SAB	2	2	0	0	0	0	0	1	0	1	0
Number of previous stillbirths	0	0	0	0	0	0	0	0	0	0	0
Final pregnancy outcome	Live birth, Full-term infant	Spontaneous abortion	Lost-to follow-up	Live birth; Preterm (36.1 weeks' gestation) infant; Small for gestational age at birth for weight	Live birth; Full-term infant	Live birth; Full-term infant; Small for gestational age at birth for weight and head circumfer-ence; Small for postnatal weight	Live birth; Preterm (35.4 weeks' gestation) infant	Lost-to follow-up	Live birth; Full-term infant	Live birth; Full-term infant	Live birth; Full-term infant

Table 34. Line Listing of Participants in Tofacitinib-Exposed Cohort

Maternal Characteris-tics	Participant #1 16043	Participant #2 89660	Participant #3 91523	Participant #4 99087	Participant #5 104006	Participant #6 105192	Participant #7 115207	Participant #8 131828	Participant #9 132031	Participant #10 137248	Participant #11 143058
Final infant outcome	No malforma-tions	N/A	Unknown	No malforma-tions	No malforma-tions	No malforma-tions	No malformatio ns	Unknown	No malforma-tions	No malforma-tions	Congenital chordee with first degree hypospadia s, Pelviectasis , hydronephr osis

Document Approval Record

Document Name:	A3921203_OTIS Tofa Preg Registry_04Mar2024_clean
Document Title:	A3921203_OTIS Tofa Preg Registry_04Mar2024_clean

Signed By:	Date(GMT)	Signing Capacity
Rubino, Heather	11-Mar-2024 13:08:34	Final Approval
De Bernardi, Barbara	11-Mar-2024 22:53:21	EUQPPV Approval

CLINICAL AND MEDICAL CONTROLLED DOCUMENT (CMCD) REQUIRED FORM/TEMPLATE		
Identifier	**Version**	**Title**
CT24-WI-GL15-RF06	2.0	NON-INTERVENTIONAL/LOW-INTERVENTIONAL STUDY TYPE 1 STUDY REPORT/MANUSCRIPT SIGNATURES

APPENDIX 1. SIGNATURES

PROTOCOL NUMBER: A3921203

TITLE OF STUDY: Tofacitinib Pregnancy Exposure Registry
FINAL STUDY REPORT VERSION: OTIS Autoimmune Diseases in Pregnancy Version 1.0

Confirmation: I confirm that this study report, which is final in content and has been printed from its definitive source, is a complete and accurate representation of the data and statistical analyses from this study.

Pfizer NI study lead/LIS1 study lead
Nana Koram, PhD

Signature: Nana Koram ebfe7534-ed25-48e3-a7f5-8448abd6e880 **Date:** 07 Mar 2024 14:42:041-0500

Principal Investigator
Christina Chambers, PhD, MPH

Signature: DocuSigned by Christina Chambers: Christina Chambers | I am the author of this document | 3/7/2024 | 10:49:14 AM PST | 3303082C148D4231BD126C92EFE7D99B **Date:** 3/7/2024

Study Information

Title	Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project
Protocol number	A3921203
Protocol version identifier	2.0
Date	24 JUN 2019
EU Post Authorization Study (PAS) register number	ENCEPP/SDPP/5703
Active substance	WHO ATC Code: L04AA29 Tofacitinb
Medicinal product	Xeljanz
Research question and objectives	What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes? <u>Objectives</u> 1. To monitor planned and unplanned pregnancies exposed to tofacitinib. 2. To evaluate the possible teratogenic effect of this medication on the primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the secondary pregnancy outcomes of spontaneous abortion, stillbirth, preterm delivery, small for gestational age, small for age for postnatal growth of live born children to one year of age. 3. To estimate the incidence of serious or opportunistic infections or malignancies in live born children up to one year of age. 4. To detect any increase in the

	prevalence or pattern of the above-mentioned outcomes among exposed pregnancies as compared with an internally generated primary comparison group of disease-matched pregnancies, and a secondary comparison group of non-diseased pregnancies, as well as compared to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program. 5. To describe pregnancy outcomes of all tofacitanib-exposed pregnancies enrolled in the exposure series (those not eligible for the cohort).
Author	Christina Chambers, PhD, MPH Professor of Pediatrics School of Medicine University of California San Diego 9500 Gilman Drive, MC 0828 La Jolla, CA 92093 Tel: +1 858-246-1704 Email: chchambers@ucsd.edu

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LIST OF TABLES

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
CDC	Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
DMARD	Disease-modifying antirheumatic drug
EDD	Estimated Date of Delivery
FDA	Food and Drug Administration
HCP	Health Care Provider
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
LMP	Last Menstrual Period
MACDP	Metropolitan Atlanta congenital Defects Program
MRHD	Maximum Recommended Human Dose
NCHS	National Center for Health Statistics
OTIS	Organization of Teratology Information Specialists
BPRER	Periodic Benefit-Risk Evaluation Report
PDA	Patent Ductus Arteriosus
PFO	Patent Foramen Ovale
PsA	Psoriatic Arthitis
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
UC	Ulcerative Colitis
US	United States

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
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Niki Palmetto, PhD, MPH	Epidemiologist	Pfizer, Inc.	235 East 42nd Street New York, NY 10017
Nana Koram, PhD, MPH	Epidemiologist	Pfizer. Inc.	235 East 42nd Street New York, NY 10017

4. ABSTRACT

Title: Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project, version 2.0, 24 June 2019.

Main author: Christina Chambers, University of California San Diego (UCSD) and the Organization of Teratology Information Specialists (OTIS)

Rationale and background: Many rheumatic diseases affect women of childbearing age. Although improvement of rheumatoid arthritis (RA) and psoriatric arthritis (PsA) disease activity spontaneously occurs in many women during pregnancy,[1,2] only a minority are reported to be in complete remission during pregnancy.[3,4] Therefore, many women still require maintenance disease-modifying drug (DMARD) therapy for their conditions, which may affect conception, pregnancy, and fetal development.[5]

Studies in women with ulcerative colitis (UC) have shown a higher risk of adverse birth outcomes compared with controls, including low birth weight, preterm delivery, and neonatal death.[6,7,8] In addition, UC active disease at the time of conception has been associated with a higher risk of disease relapse during pregnancy.[8,9]

Tofacitinib is an oral janus kinase (JAK) inhibitor and is currently approved in the US for adults with moderately to severely active RA and active PsA who have had an inadequate response to or intolerance to methotrexate or other DMARDs, and for the treatment of adults with moderate to severely active UC. Human pregnancy exposure data for tofacitinib is limited; however tofacitinib is likely to be utilized by pregnant women when they and their doctors believe that risk/benefit considerations favor its use. Also, given the frequency of unplanned pregnancies, information regarding the safety of tofacitinib in human pregnancy is essential from a public health perspective.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the Food and Drug Agency (FDA).

Research question and objectives: What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes? The objectives of the Tofacitinib Pregnancy Exposure Registry are to:

1. Monitor planned and unplanned pregnancies exposed to tofacitinib.

2. To evaluate the potential teratogenic effect of this medication relative to the primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the secondary pregnancy outcomes of spontaneous abortion, stillbirth, preterm delivery, small for gestational age, and small for age for postnatal growth of live born children to one year of age.

3. To estimate the incidence of serious or opportunistic infections or malignancies in live born children up to one year of age.

4. To detect any increase in the prevalence or pattern of the above mentioned outcomes among exposed pregnancies as compared with an internally generated primary comparison group of disease-matched pregnancies, and a secondary comparison group of non-diseased pregnancies, as well as compared to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program,[10] and

5. To describe pregnancy outcomes of all tofacitanib-exposed pregnancies enrolled in the exposure series (those not eligible for the tofacitinib-exposed cohort).

Study design: This is a prospective, observational, exposure cohort study of pregnancy and infant outcomes in women with a disease for which tofacitinib has an approved indication and enrolled in the registry prior to 20 weeks from the first day of the last menstrual period (LMP). The birth prevalence or incidence of outcomes in women exposed to tofacitinib within first 12 weeks post LMP and their infants will be compared to those observed in 2 unexposed comparator groups: a disease-matched comparison group of women who have not used tofacitinib during pregnancy (disease comparison group), and a comparison group of healthy women who do not have an autoimmune disease, have not had exposure to a known human teratogen, and have not taken tofacitinib in pregnancy (healthy comparison group).

Population: The study population includes pregnant women who reside in the U.S. or Canada, who do or do not have a disease for which tofacitinib has an approved indication, and have or have not used tofacitinib for any length of time in pregnancy.

Three groups of participants will be enrolled in the study cohort prior to 20 weeks gestation and followed for pregnancy and infant outcomes:

- Pregnant women with an approved indication exposed to tofacitinib within the first 12 weeks post-LMP;

- Pregnant women with an approved indication not exposed to tofacitinib during pregnancy;

- Pregnant women who do not have an autoimmune disease, have not had exposure to a known human teratogen, and have not taken tofacitinib during pregnancy.

Another group of participants who are tofacitinib-exposed but do not meet cohort study selection criteria will be enrolled in the exposure series.

Variables: Exposure will be defined as tofacitinib treatment by maternal report and verified by medical record review, with detailed information on the gestational timing, route of administration, dose, and dates of exposure. Outcome variables include major structural birth defects, spontaneous abortion, stillbirth, elective termination for any reason, preterm delivery, infant birth size, postnatal growth of live born children up to one year of age, and serious or opportunistic infections or malignancies in live born children up to one year of

age. These will be obtained by maternal report and verified by medical record review. Potential confounders or covariates to be collected include maternal age, race/ethnicity, socioeconomic status, pregnancy and health history, lifestyle factors, comorbidities, medication, vaccine and vitamin/mineral exposures, prenatal tests, measures of disease severity, as well as indication.

Data sources: Data will be collected using maternal interviews, medical records (obstetric, delivery hospital, pediatric, rheumatologist, dermatologist, gastroenterologist, and/or other specialty provider), and pregnancy exposure diary. Maternal interview data will be recorded on hard copy forms, and medical record abstraction data will be recorded on electronic forms, which will be retained by OTIS. Maternal interview forms are considered the primary data sources for the study. Data from these forms will be extracted and entered into a customized OTIS study database located at the OTIS Research Center and developed specifically for the OTIS studies.

Study size: The target sample size for the study is 300 pregnant women; 100 pregnant women in each of the three cohort groups: tofacitinib-exposed, disease-matched unexposed, and non-diseased unexposed.

Data analysis: Demographic and baseline characteristics will be compared between the cohorts. The primary analysis will be a comparison of the prevalence rate of major structural birth defects in live born infants between the tofacitinib-exposed cohort and the disease-matched unexposed cohort. Where numbers permit, multivariable analyses will be conducted to determine the relationship of tofacitinib with the primary outcome of major structural birth defects, and the secondary outcomes of small for gestational age, preterm delivery, spontaneous abortion, stillbirth, elective termination and small for age postnatal growth, as numbers permit.

Milestones: The study was originally planned for five years. In 2019, the protocol was amended to include any approved indication, and the data collection timeline was extended for an additional five years, with a final study report and analysis projected for March 2024. An interim report will be reviewed by the Scientific Advisory Board and Sponsor annually. The final report with statistical analysis according to the statistical analysis plan will be prepared at the end of the study.

5. AMENDMENTS AND UPDATES

Amend-ment number	Date	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
1	24 Jun 2019	9.2.2	Inclusion of any approved tofacitinib indication in the exposed and disease comparison groups	Tofacitinib has recently received FDA approval for indications of psoriatic arthritis and ulcerative colitis. This is in addition to the previously approved rheumatoid arthritis indication. The protocol has been amended to include indications as they are approved.
1	24 Jun 2019	6	Amended final study report date from 31 Aug 2018 to 30 Mar 2024	Data collection and study report milestones extended to accommodate new indications, and continue data collection for RA indication, given low recruitment to date.
1	24 Jun 2019	Global	Edited protocol to adapt to new Pfizer protocol template	A new CT24 template had been approved since approval of initial protocol.

6. MILESTONES

Milestone[1]	Planned date
Original Contract Signed	31 July 2013
IRB Approval	31 August 2013
Start of data collection	01 November 2013[2]
End of data collection	30 September 2023
Registration in the EU PAS register	20 February 2014
Final study report	30 March 2024

[1] Annual study progress reports and mid-year recruitment and malformation table update reports will be included within the periodic benefit-risk evaluation report (PBRER) cycle for tofacitinib.
[2] This is the original start date of data collection for the rheumatoid arthritis indication. Planned start of data collection for PsA and UC indication is May 2019.

7. RATIONALE AND BACKGROUND

Many rheumatic diseases affect women of childbearing age potential and the medications used to treat these diseases may affect conception, pregnancy, and fetal development (Skomsvoll, 2001).[5] Although improvement of rheumatoid arthritis (RA) and psoriatic arthritis (PsA) disease activity spontaneously occurs in a proportion of pregnancies many women still require maintenance disease-modifying drug (DMARD) therapy for their conditions. There is some suggestion that women with RA have decreased fecundity (probability of conception) and decreased fertility (ability to conceive) (Nelson, 1997).[1] However, there is no strong evidence that suggests an association between RA and adverse fetal outcome (Nelson, 1997).[1] Disease activity seems to improve in many women with RA during pregnancy, however only a minority are reported to be in complete remission during pregnancy (Barrett et al, 1999; de Man et al, 2008).[3,4] In 80% of women with psoriatic arthritis (PsA), the disease improved during pregnancy (Ostensen, 1992).[2] Children born to mothers with inflammatory arthritis have an increased incidence of preterm birth,small for gestational age, low birth weight, increased perinatal mortality and congenital malformations (Skomsvoll, 1999).[11] A 3.5% birth defect rate was reported in Norwegian women with specified and non-specified inflammatory arthritis including rheumatoid arthritis. However, the actual number of women with rheumatoid arthritis in this population may not be clear (Skomsvoll, 1999).[11] These adverse outcomes may be related to the underlying autoimmune disease or to concomitant rheumatic therapy. The safety of taking most anti-rheumatic drugs during pregnancy is not clear since experience in humans is usually anecdotal.

Studies in women with ulcerative colitis (UC) have shown a higher risk of adverse birth outcomes compared with controls, including low birth weight, preterm delivery, and neonatal death (Cornish, 2007, Stephansson, 2011, Mahadevan, 2018).[6,7,8] In addition, UC active disease at the time of conception has been associated with a higher risk of disease relapse during pregnancy (de Lima-Karagiannis, 2016, Mahadevan, 2018).[8,9]

Tofacitinib is an oral janus kinase (JAK) inhibitor and is currently approved in the US for adults with moderately to severely active RA and active PsA who have had an inadequate response to or intolerance to methotrexate or other DMARDs, and for the treatment for of adults with moderate to severely active UC. For RA, it may be used in combination with methotrexate or in monotherapy. Additionally, tofacitinib is approved for RA, PsA, and UC in Canada, the EU, and other global regions.

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a commitment to the U.S. Food and Drug Administration (FDA).

8. RESEARCH QUESTION AND OBJECTIVES

What is the risk of maternal use of tofacitinib during pregnancy on pregnancy and birth outcomes?

8.1. Objectives

1. To monitor planned and unplanned pregnancies exposed to tofacitinib.

2. To evaluate the possible teratogenic effect of tofacitinib relative to primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the secondary pregnancy outcomes of spontaneous abortion, stillbirth, preterm delivery, small for gestational age, small for postnatal growth of live born children to one year of age.

3. To estimate the incidence of serious or opportunistic infections or malignancies in live born children up through one year of age.

4. To detect any increase in the prevalence or pattern of the above-mentioned outcomes among exposed pregnancies as compared with an internally generated primary comparison group of disease-matched pregnancies, and a secondary comparison group of non-diseased pregnancies, as well as compared to external data from the Centers for Disease Control and Prevention (CDC) Metropolitan Atlanta Congenital Defects Program (MACDP), a population-based birth defects surveillance program.[10]

5. To describe pregnancy outcomes of all tofacitinib-exposed pregnancies enrolled in the exposure series (see Section 9.2.4) (those not meeting inclusion/exclusion criteria (Section 9.2.2 and Section 9.2.3) for the tofacitinib-exposed cohort).

9. RESEARCH METHODS

9.1. Study Design

This is a prospective, observational cohort study of pregnancy outcomes in women with a disease for which tofacitinib has an approved indication who are exposed to tofacitinib during pregnancy compared to pregnancy outcomes in women with these same indicated diseases who have not been exposed to tofacitinib during pregnancy (disease-matched unexposed comparison group), and pregnancy outcomes in women without an autoimmune disease (non-diseased unexposed comparison group). Women with exposure to tofacitinib

during pregnancy who do not meet the eligibility criteria will be enrolled into the exposure-series (Section 9.2.3).

9.2. Setting

The cohort study will be conducted by the Organization of Teratology Information Specialists (OTIS) which is a network of university and health department based telephone information centers serving pregnant women and healthcare providers throughout North America.[12] These services receive spontaneous telephone inquiries from women and health care providers about the safety or risk associated with environmental exposures in pregnancy, including medications. Trained Teratogen Information Specialists at each site provide appropriate risk assessment and referral for all patient and health care provider callers free of charge. These services also provide a basis for collaborative research such as this Registry. Thus, individual Teratogen Information Services located throughout the U.S. and Canada will serve as a source of referrals not only for tofacitinib-exposed pregnancies but also for similarly-ascertained pregnant women with an approved indicated disease who have not used tofacitinib and similarly ascertained pregnant women without an autoimmune disease who have not used tofacitinib or any known human teratogen. As OTIS member services receive over 70,000 teratogen information telephone inquiries per year, OTIS members constitute a major source of identification and recruitment of exposed women and appropriate comparison women. Once women are in contact with the Registry Coordinating Center, enrollment in the Registry is voluntary and requires informed consent of the pregnant woman. The Registry will enroll pregnant women who are less than 20 weeks' gestation. This is accomplished by encouraging clinicians to refer patients, and following-up with women who are planning pregnancy who contact an OTIS service or who self-refer, and direct outreach efforts to target women who are less than 20 weeks' gestation. These efforts reduce possible bias based on prior knowledge of a normal ultrasound, and allow for better estimation of risk of spontaneous abortion.

The study population includes pregnant participants with a disease for which tofacitinib has an approved indication with exposure to tofacitinib during pregnancy, and two comparison groups without tofacitinib exposure during pregnancy (one disease-matched unexposed comparison group, and one non-diseased unexposed comparison group) who reside in the U.S. or Canada. With the addition of the approved indications, it is anticipated that approximately 20 pregnant women with exposure to the tofacitinib could be enrolled in the Registry each year of the additional five-year recruitment period.

9.2.1. Analysis Population ("cohort analysis")

Although the Registry will collect and follow up on reports of all types (ie, retrospective, paternal, off-label indication, etc.) involving pregnancy exposure to tofacitinib, regardless of inclusion/exclusion criteria ("exposure case series"), the core of the Registry will be a multicenter prospective cohort study ("cohort analysis") designed to ascertain and follow-up on cohort-eligible (meeting all inclusion and exclusion criteria) exposures to tofacitinib and to compare these to two internally-generated comparison groups and one external comparison group.

- Comparison Group I consisting of pregnant women who have a disease for which tofacitinib has an approved indication but did not take tofacitinib, including a subgroup of women who have taken an anti-TNF medication during pregnancy.

- Comparison Group II consisting of pregnant women who contact an OTIS member service and who do not have an autoimmune disease nor have exposure to any known teratogens. This will be a secondary comparison group.

Regarding the risk of major structural defects (primary outcome) among tofacitinib users, an external comparison will also be made to the Metropolitan Atlanta Congenital Defects Program (MACDP), which is a population-based birth defects surveillance program in the U.S. with careful follow-up and classification of major structural defects identified up to six years of age. This particular program is considered appropriate for external comparison given the fact that it is population based and includes a relatively high level of validation of reported defects identified in children up to six years of age. The overall rate of major structural defects identified in the MACDP (approximately 3% in 2005) is comparable to the overall rates (2-3%) identified in larger samples of Teratogen Information Service cohort studies that involve a careful review of medical records and physician examinations.

9.2.2. Inclusion Criteria for "Cohort Analysis" Group

The study will enroll women in three cohorts:

1. **Tofacitinib-Exposed Group- Inclusion Criteria.**

    - Currently pregnant women who have had an exposure to tofacitinib, for the treatment of a disease for which tofacitinib has an approved indication, for any number of days, at any dose, and at anytime from the 1st day of the last menstrual period up to and including the 12th week after the first day of the last menstrual period (LMP). If the date of LMP is unclear, or if a first-trimester ultrasound has been done and the estimated date of conception is more than one week discrepant from the menstrual period calculation, the first-trimester ultrasound-derived date will be used to calculate a date for LMP and conception, and

    - Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and

    - Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

2. **Comparison Group I: Disease-matched Unexposed (to tofacitinib) Cohort – Inclusion Criteria.**

   - Currently pregnant women with a diagnosis of a disease for which tofacitinib has an approved indication, by maternal report and validated by medical records, who have not taken tofacitinib any time since first day of last LMP to delivery in the current pregnancy but who may or may not have taken another medication for their disease including an anti-TNF or other biologic in the current pregnancy. To the extent that tofacitinib-exposed women enrolled in the cohort study also have methotrexate exposure, women in the disease-matched unexposed comparison group I with methotrexate exposure will be recruited to frequency match the number with tofacitinib plus methotrexate, and

   - Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and

   - Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

3. **Comparison Group II: Non-diseased Unexposed (to tofacitinib) Cohort -Inclusion Criteria.**

   - Currently pregnant women who have not had exposure to a known human teratogen or biologic agent as confirmed by the OTIS Research Center, and

   - Currently pregnant women who do not have an autoimmune disease,

   - Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and

   - Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.

9.2.3. Exclusion Criteria for "Cohort Analysis" Group

Patients meeting any of the following criteria will not be included in the analytic component of the study:

1. **Tofacitinib-Exposed Group- Exclusion Criteria.**

    - Currently pregnant women who have had an exposure to tofacitinib during pregnancy but have also had an exposure to one or more of the following (either known human teratogens or medications of unknown safety used for the same indication) during the index pregnancy will not be qualified as subjects for the tofacitinib-exposure group in the cohort study:

        - Chlorambucil;
        - Cyclophosphamide;
        - Mycophenylate mofetil;
        - Adalimumab;
        - Abatacept;
        - Certolizumab pegol;
        - Etanercept;
        - Tocilizumab;
        - Infliximab;
        - Golimumab;
        - Vedolizumab;
        - Secukinumab;
        - Ustekinumab;
        - Ixekizumab;
        - Or leflunomide within one year prior to conception unless a documented blood level below the detectable limit prior to enrollment is available;

    - Women who have first contact with the project after prenatal diagnosis of any major structural defect,

    - Women who have enrolled in the cohort study with a previous pregnancy,

- Women who have used tofacitinib for an indication other than an approved indicated disease,

- Note: Retrospective cases will be followed (see subsequent sections), but will not be included in the cohort study.

2. Comparison Group I – Exclusion Criteria

- Currently pregnant women who have had an exposure to the medications listed below that are known or suspected human teratogens:

  - Chlorambucil;

  - Cyclophosphamide;

  - mycophenylate mofetil;

  - or leflunomide within one year prior to conception unless a documented blood level below the detectable limit prior to enrollment is available,

- Women who have first contact with the project after prenatal diagnosis of any major structural defect,

- Women who have enrolled in the cohort with a previous pregnancy.

3. Comparison Group II – Exclusion Criteria

- Currently pregnant women who incur an exposure to a known teratogen in the first trimester after the time of enrollment will be disqualified as subjects for purposes of the analysis,

- Women who have a diagnosis of an autoimmune disease,

- Women who have first contact with the project after prenatal diagnosis of any major structural defect,

- Women who have enrolled in the cohort study with a previous pregnancy.

9.2.4. Tofacitinib-exposed Pregnancies not Eligible for the Cohort Study ("exposure series")

By study design, pregnancies that do not meet the exposed cohort criteria for reasons described in Section 9.2.2. and 9.2.3 will be excluded from the cohort analysis, however, information on their birth outcomes can be useful for hypothesis generating when reviewing the cohort data. For this reason, women who do not meet the exposed cohort criteria will be invited to enroll in a separate "exposure series".

With informed consent, data will be collected from maternal questionnaires, medical records review and the physical examination using the same protocol as the cohort study to the extent possible.

9.2.5. Modalities of Recruitment

All exposed subjects and comparison subjects will be recruited through spontaneous callers to participating OTIS member services in locations throughout North America and through active recruitment strategies, eg, direct mailings to specialist, obstetric health care providers, pharmacists, web site, and professional meetings. Each OTIS service will provide exposure counseling in the routine manner for all exposed and unexposed women who initially make contact with the service with questions regarding a current pregnancy. Subsequently, each OTIS service will explain the study protocol to potentially eligible participants, and then will request permission to refer to the Research Center at the University of California, San Diego. Potential subjects who agree to be referred will contact the Research Center or be contacted if they prefer. OTIS member services will also refer callers to the Research Center whose exposure to tofacitinib does not appear to qualify for the cohort study (eg, post first trimester exposure,retrospective reports), as these will be handled as Exposure Case Series (See Section 9.2.3). Health care providers can also contact the Registry and refer patients; however, in all cases the mother is the individual who provides informed consent for participation and completes the interview-based data collection.

9.3. Variables

This study uses secondary data that is routinely collected as part of the OTIS Pregnancy Registy. Table 1 provides a description of variables to be included in this study.

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Exposure to tofacitinib	Exposure	Maternal report Medical record	Maternal report of exposure to tofacitinib of at least one dose any time from first day of last menstrual period (LMP) to end of pregnancy. Confirmation of exposure with medical records.
Dose of tofacitinib	Exposure	Maternal report Medical record	Dose of tofacitinib in mg per day (maternal report and confirmation with medical records).
Duration of tofacitinib use	Exposure	Maternal report Medical record	Weeks of tofacitinib use in pregnancy (maternal report and confirmation with medical records).

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Indication	Exposure	Maternal report Medical record	Indication for use of tofacitinib (maternal report and confirmation with medical records).
Major structural birth defect	Outcome - primary	Maternal report Medical record OTIS investigator review Dysmorphological Evaluation	The Registry adopts the term "major structural defect" (ie,birth defect) for an abnormality usually referred to as a "congenital abnormality" and defines major structural defect as follows: • Any major structural or chromosomal defect defined and classified, using the CDC Metropolitan Atlanta Congenital Defects Program (MACDP) classification of birth defects (CDC 2017). The CDC guidelines disqualify as major structural defects: • Those findings that are present in infants with outcomes at <36 weeks gestational age or if gestational age is unavailable, weighing <2500 grams, and are attributed to prematurity alone, such as patent ductus arteriosus (PDA), patent foramen ovale (PFO), and inguinal hernias. • Infants with only transient or infectious conditions, or biochemical abnormalities, are classified as being without major structural defects unless there is a possibility that the condition reflects an

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
			unrecognized major structural defect.
Minor structural defect	Outcome - secondary	Maternal report Dysmorphology Evaluation	A defect which occurs infrequently in the population but which has neither cosmetic nor functional significance to the child and is identified using a study-related checklist incorporated into the study dysmorphology examination of live born infants.
Spontaneous abortion	Outcome - secondary	Maternal report Medical record	Non-deliberate embryonic or fetal death that occurs prior to 20.0 weeks' gestation.
Stillbirth	Outcome - secondary	Maternal report Medical record	A non-deliberate fetal death that occurs at or after 20.0 weeks' gestation but prior to delivery.
Premature delivery	Outcome - secondary	Maternal report Medical record	A spontaneous or induced delivery at <37 gestational weeks (as counted from LMP), reported by the mother and validated through the medical record.
Small for gestational age	Outcome - secondary	Maternal report Medical record	Birth size (weight, length or head circumference) $\leq 10^{th}$ percentile for sex and gestational age using National Center for Health Statistics (NCHS) pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants will be used for premature infants (Olsen 2010).[16]

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Postnatal growth deficiency	Outcome - secondary	Medical record	Postnatal size (weight, length or head circumference) $\leq 10^{th}$ percentile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for premature infants.
Lost-to-follow-up	Outcome - secondary	Telephone attempts Mail/Email contact attempts Maternal report	An enrolled subject who withdraws or who fails to complete the outcome interview despite a standard number of telephone attempts and attempt to contact by mail as per study procedure manual within one year of the mother's estimated due date.
Serious or opportunistic infection	Outcome - secondary	Maternal report Medical record	Defined as those in appendices and infections requiring hospitalization, identified in newborn infants up to one year of age.
Malignancy	Outcome - secondary	Maternal report Medical record	Any malignancy reported in an infant up to one year of age.
Age	Confounder	Maternal report	Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34).
Race	Confounder	Maternal report	Maternal/Paternal race (Caucasian/White, Black, Asian/Pacific Islander, Native American, Other).
Ethnicity	Confounder	Maternal report	Maternal/Paternal ethnicity (Hispanic, Non-Hispanic).
Education	Confounder	Maternal report	Maternal Educational Category (years of completed education <12, 12-15, >15).

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Socioeconomic Category	Confounder	Maternal report	Hollingshead Socioeconomic Category based on maternal and paternal occupation and education (1-5).
Height	Confounder	Maternal report	Maternal height (cm).
Pre-pregnancy body weight	Confounder	Maternal report Medical record	Maternal pre-pregnancy body weight (kg) (confirm with medical record).
Pre-pregnancy BMI	Confounder	Maternal report	Maternal pre-pregnancy BMI (<18.5, 18.5-24.9, 25-29.9, >=30).
Number of times pregnant	Confounder	Maternal report Medical record	Number of times ever pregnant (1, 2-3, 4-5, >=6) (confirm with medical record).
Previous live birth or stillbirth deliveries	Confounder	Maternal report Medical record	Number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, >=5) (confirm with medical record).
Previous pregnancies ending in spontaneous abortion	Confounder	Maternal report Medical record	Number of previous pregnancies ending in spontaneous abortion (0, 1, 2, >=3) (confirm with medical record).
Previous pregnancies ending in elective termination	Confounder	Maternal report Medical record	Number of previous pregnancies ending in elective termination (0, 1, 2, >=3) (confirm with medical record).
Gestational age	Confounder	Maternal report Medical record	Weeks of pregnancy at time of enrollment, continuous and categorical (<13, 13-19.9, >=20): gestational age is calculated from the first date of LMP.
Referral source	Confounder	Maternal report	Source options: Sponsor, OTIS service, HCP, Internet, Other.

Table 1. Variables

Variable	Role	Data source(s)	Operational definition
Geographic area of residence	Confounder	Maternal report	Geographic area of residence (eg, US, Canada).
Disease Symptom/Severity measures	Confounder	Maternal report	Disease Symptom/Severity measures (exposed and disease-matched cohorts only).
Prenatal, Multivitamin, or Folic acid	Confounder	Maternal report	Prenatal, Multivitamin or Folic Acid supplement use by timing (began prior to conception, post-conception only, not taken at all).
Alcohol use in pregnancy	Confounder	Maternal report	Yes/No. Dose and frequency are captured.
Tobacco use in pregnancy	Confounder	Maternal report	Yes/No.
Prenatal diagnostic tests prior to enrollment	Confounder	Maternal report Medical record	Tests performed prior to enrollment (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis).
Prenatal diagnostic tests anytime during pregnancy	Confounder	Maternal report Medical record	Tests performed anytime in pregnancy (Ultrasound level 1, Ultrasound level 2, Chorionic Villus Sampling, Amniocentesis).
Maternal pregnancy exposure to another known human teratogen	Confounder	Maternal report Medical record	Maternal pregnancy exposure to another known human teratogen (eg, methotrexate) (confirm with medical record).
Years since diagnosis of approved indicated disease	Confounder	Maternal report Medical record	Years since diagnosis of approved indicated disease.

Abbreviations: BMI = body mass index; CDC = Centers for Disease Control and Prevention; cm = centimeters; kg = kilograms; HCP = health care provider; LMP= last menstrual period; MACDP= Metropolitan Atlanta Congenital Defects Program; NCHS = National Center for Health Statistics; OTIS = Organization of Teratology Information Specialists; US = United States.

The Statistical Analysis Plan (SAP) will provide greater detail on the definitions of, the identification of and the controlling for confounders and/or effect modifiers.

9.4. Data Sources

The OTIS Research Center is responsible for verifying the subject selection criteria, enrolling each subject and securing informed consent, oral and written (when available or applicable), providing all pregnancy (intake/enrollment and interim I and II) and post-partum follow-up interviews and medical record review, scheduling dysmorphological physical examinations, recording and storage of all data, and subsequent data analysis and interpretation.

9.4.1. Intake/Enrollment Interview

Following oral administration of informed consent, a structured maternal intake telephone interview will be conducted by a trained Research Associate at the OTIS Research Center. This interview will include questions on the following: pregnancy history; current health history; pre-pregnancy weight and height; socioeconomic and demographic information including maternal and paternal occupation, education and ethnicity; income category, current medication use, both prescriptive and over the counter; other environmental or occupational exposures, alcohol, tobacco, caffeine and illicit drug use; current pregnancy complications including illnesses; names and addresses of health care providers; and history of onset and other characteristics of an approved indicated disease if applicable. Women with an approved indicated disease will be asked to respond to an appropriate severity assessment questionnaire/quality of life questionnaire which is a validated measure of disease severity or quality of life that has been used in the current OTIS Autoimmune Diseases in Pregnancy Project as a means of assessing the potential contribution of severity of disease as represented by maternal symptoms to pregnancy outcome. Once the intake interview is complete, an enrollment packet will be sent to the participant including a written consent for signature, the U.S. Health Insurance Portability and Accountability Act (HIPAA) Authorization Addendum (when applicable), an obstetric medical record release form, and a diary to record information about any exposures or prenatal testing during pregnancy.

9.4.2. Interim Interviews I and II (20 and 32 Weeks' Gestation)

Women who have enrolled in the study prior to 18 weeks post-LMP will be interviewed by telephone at 20-22 weeks post-LMP, 32-34 weeks post-LMP and within two to six weeks after the expected due date. Women who have enrolled between 19 and 20 weeks post-LMP will be interviewed at 32-34 weeks post-LMP (See Table 2 Timing of Cohort Enrollment, Interviews, Examinations, Medical Record Request and Review).

The purpose of these interviews will be to update records of pregnancy exposures and results of prenatal tests, administer the severity assessment (when applicable) to remind women to maintain the exposure diary, to update phone number and address information, and to determine if the pregnancy has ended prior to the expected due date.

9.4.3. Pregnancy Outcome Interview

At any of the interim interview points, if the pregnancy has ended, the outcome interview will be conducted at this time or at the earliest convenient time for the mother. For women who are still pregnant at the 32-34 week interview, the outcome interview will be conducted within 0 to six weeks after the expected due date.

The outcome interview for live born infants will be a structured telephone interview and information will be elicited on the following: date of delivery, hospital location and mode of delivery; sex, birth weight, length and head circumference; Apgar scores; description of delivery or birth complications including malformations; type and length of hospital stay for mother and infant; delivering physician's and infant physician's names and addresses; method of infant feeding; pregnancy weight gain; and additional exposures and results of prenatal tests occurring since the previous interview.

The outcome interview for spontaneous or elective abortions will also be structured and information will be elicited on the following: date and type of outcome; hospital location if applicable; prenatal diagnosis; pathology results if available; and additional exposures and results of prenatal tests occurring since the previous interview. The outcome interview for stillborn infants will include all of the above plus information on sex, birth size and autopsy results if available.

Adverse pregnancy outcomes related to study endpoints will be reported to Pfizer as part of the annual study report; major structural defects, spontaneous abortions, elective terminations, fetal or neonatal deaths occurring in the tofacitinib-exposed group will be reported to the Sponsor within 24 hours of the Research Center staff learning of the event. These reports will be made using the FDA's MedWatch form. Pfizer will be responsible for directly reporting to the FDA for events involving their product according to regulatory guidelines.

9.4.4. Medical Records and General Pediatric Evaluation

Upon completion of the outcome interview, each woman will be mailed a packet containing medical records release forms for the delivery hospital, obstetrician, pediatrician, and spcialist if applicable. For women whose pregnancies have ended in spontaneous or elective abortion or stillbirth, records release forms will be mailed for the specialist's evaluation, if applicable, and if prenatal diagnosis, pathology or autopsy reports are available. Each woman will be asked to sign the forms and to return them along with the pregnancy exposure diary form.

Upon receipt of the signed medical records release forms, a standard physical evaluation form will be mailed to each pediatrician or other physician responsible for the care of each live born infant. This form includes information on infant size at the time of the latest examination and an open-ended question about postnatal complications and congenital anomalies.

At one year of age, another medical records release form for the pediatrician, or health care provider caring for the child, is sent to the mother for signature. The signed form with a standard physical evaluation form is sent to the health care provider to request updated information on growth, major structural defects, any serious or opportunistic infections, hospitalization, and/or malignancies.

9.4.5. Dysmorphological Evaluation

Live born infants will be examined by one of a team of study-dedicated dysmorphologists, led by Co-Investigator, Kenneth Lyons Jones, M.D., from the University of California, San Diego, all licensed pediatricians with subspecialty fellowship training in dysmorphology/genetics. This team of physicians has been functioning as the specialist examiners for the current OTIS Autoimmune Diseases in Pregnancy Project and have completed examinations for well over 1,500 infants throughout North America as part of this protocol using the same standard procedures as are incorporated in this Registry. The physical examinations evaluate infants for both major and minor structural defects which provide increased sensitivity for detecting a specific pattern of malformation should one exist (See Section 9.5 for sample size and power). All infants will be examined within the first year of life or as soon as the examination can be practically arranged, as is the protocol in the existing OTIS Autoimmune Diseases in Pregnancy Project. The Research Center will group and schedule these follow-up examinations to meet the study criteria of infant age, to maximize physician blinding as to exposure status, and to minimize travel time and expense.

Infant examinations will be conducted using a standard checklist of approximately 130 minor malformations included in a standard physical evaluation form. In addition, in the tofacitinib-exposed group and in the disease-matched comparison group, digital photographs of the infant's minor malformations will be taken to aid in validating any findings across examiners.

Dysmorphologists will perform these examinations blinded to the exposure or comparison group status of the mothers. Because subjects with autoimmune diseases such as RA and PsA frequently have visible evidence of the disease, the use of a disease-matched comparison group allows for preservation of physician blinding.

Table 2. Timing of Cohort Enrollment, Interviews, Examinations, Medical Record Request and Review

	<20 weeks gestation	20-22 weeks gestation*	32-34 weeks Gestation	0-6 weeks after delivery	0-12 months after delivery	1 year after delivery
Referral	√					
Enrollment and Consent	√					
Intake Interview	√					
Interim Interview I		√				
Interim Interview II			√			
Outcome Interview				√		
Dysmorphological Examination					√	
Medical Record Request and Review				√	√	√
Pediatric Medical Record Review and Questionnaire at 1 Year						√

*If subject is enrolled and Intake Interview is conducted between 19 and 20 weeks' gestation, only one Interim Interview will be conducted during pregnancy at 32-34 weeks' gestation.

9.4.6. Outcome Classification for Structural Defects for Cohort Study

The method for classifying structural defects for purpose of analysis has been previously described by the study investigators and the OTIS Research Group[13,10] and has been used in previous studies conducted by this group, including all current OTIS Autoimmune Diseases in Pregnancy Project.

9.4.6.1. Criteria for Structural Defects – Counted/Included

- *Time period for identification:* major structural defects identified up to one year of age by the mother, the health care provider, or identified in the dysmorphological examination will be included in the primary analysis. Defects identified after that time frame will be described and considered separately.

- *Confirmation of defects:* independent confirmation of certain defects will be required. For example, a heart murmur thought to represent a ventricular septal defect that is ascertained by the examining dysmorphologist prior to one year of age will be included if it is confirmed as a heart defect by cardiac ultrasound. Similarly, a midline cutaneous marker at L2-L3 noted in the dysmorphological examination will be included as occult spinal dysraphism only if confirmed by appropriate imaging studies. In addition, minor structural defects that are reported only by the mother or medical record but not confirmed by the dysmorphological examination will not be included as valid defects.

- *Body measurements:* only those growth parameters for which actual measurements are available will be considered in the analysis. Measurements of head circumference, length, weight, palpebral fissure length, inner canthal distance, ear length, and philtrum length will be taken. These will be compared to mean values for infants of the same age and sex (where sex-specific normative data are available). Less than or greater than two standard deviations from the mean will be used to define such terms as microcephaly, hypertelorism, etc.

9.4.6.2. Criteria for Structural Defects – Not Counted/Excluded

- *Birthmarks:* isolated birthmarks will not be included as defined by the MACDP.[14]

- *Variations of normal:* features on the physical examination which occur in greater than 4 percent of the population and have no cosmetic or functional significance for the child, eg, 2,3 syndactyly of the toes less than one-third of the distance to the tip of the 3rd phalanx, will not be included.

- *Deformational defects:* Those deformational defects that do not require casting or surgery will not be included.

- *Time period for identification:* structural defects ascertained after 12 months of age will not be included in the analysis, but will be considered separately in the context of a possible pattern.

- *Defects identified in spontaneous abortions or elective terminations:* Defects identified by prenatal ultrasound or examination of the products of conception following elective or spontaneous abortion will be not be included in the primary analysis due to potential bias involved in non-uniform use of prenatal diagnosis and pathology evaluation for all abortuses; however, these defects will be considered in a separate analysis including all defects in the numerator over all pregnancies with known outcome in the denominator, and in the context of pattern.

9.4.7. Outcome Classification for Secondary Endpoints for Cohort Study

9.4.7.1. Definitions for Secondary Endpoints

- *Spontaneous abortion:* spontaneous abortion is defined as non-deliberate fetal death which occurs prior to 20.0 weeks post-LMP.

- *Elective abortion:* elective abortion is defined as deliberate termination of pregnancy at any time in gestation.

- *Stillbirth:* stillbirth is defined as non-deliberate fetal death anytime in gestation at or after 20.0 weeks post-LMP.

- *Premature delivery:* premature delivery is defined as live birth prior to 37.0 weeks gestation as counted from last menstrual period (or calculated from first-trimester ultrasound-derived due date if last menstrual period uncertain or more than one week discrepant). Elective caesarian deliveries or inductions prior to 37.0 weeks will be considered separately.

- *Small for gestational age:* small for gestational age is defined as birth size (weight, length or head circumference) less than or equal to the 10th centile for sex and gestational age using standard pediatric CDC growth curves for full term or preterm infants.[15,16,17]

- *Postnatal growth deficiency:* postnatal growth deficiency is defined as postnatal size (weight, length or head circumference) less than or equal to the 10th centile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for premature infants if the postnatal measurement is obtained at less than one year of age.

- *Lost-to-follow-up:* Subjects will be considered lost-to-follow-up if they have completed the initial intake interview but subsequently fail to complete the outcome interview and medical records release despite repeated attempts after one year of the mother's estimated due date. Voluntary subject withdrawals will be considered separately.

- *Postnatal serious opportunistic infections, hospitalizations, or malignancies:* Through the one-year postnatal follow-up period, pediatric records will be requested with specific requests for documentation of serious opportunistic infections, hospitalizations or malignancies. Serious opportunistic infections are listed in Annex I.

9.4.8. Monitoring of Outcomes

9.4.8.1. Monitoring Methods

The intent of the Registry is to determine whether there is a signal that might indicate a potential risk of major structural defects in the offspring of pregnant women following an exposure to tofacitinib during pregnancy. The major strength of the Registry is that the cohort data is collected before known outcome of pregnancy with comparison to two appropriate comparison groups that are internally and contemporaneously generated. Furthermore, the prospective cohort study includes a level of outcome evaluation with a dysmorphological examination that exceeds that of any other method.

Reports outside of the cohort ("exposure case series"), can be used to illuminate knowledge gained from the cohort study. Therefore, it is necessary to determine in the evaluation of the cumulative data of all types, what the indicators of a signal or pattern are, and what course of action will be taken if a signal is noted. The cohort analysis may never have sufficient sample size to detect a teratogenic effect for a particular rare outcome following exposure to tofacitinib. However, the Registry Advisory Committee will develop a plan for determining

what constitutes a signal for a major structural defect, how it is reviewed, and what action might be taken should such a signal be seen. The Advisory Committee will review the data annually in the context of the annual interim report and will review the final report and analysis. The Advisory Committee is also available for ad hoc consultation, data review, and advice.

9.5. Study Size

Recruitment goals are set at 1-20 subjects per year in each of the three groups as shown below in Table 3 based on recruitment to date in each group (Year 1-5 actual, Year 6-10 projected). The sample size is based on estimates that may require revision as the study progresses. The sample size for the study is projected to be 300 participants for all indications and all cohort groups. However, if the sample size is met prior to the pre-determined recruitment end date, recruitment will continue during the allotted recruitment period to allow for 300 participants per indication and cohort group.

Table 3. Recruitment Timetable and Sample Size

Year/Cohort Group	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8	Year 9	Year 10
Exposed (Cohort I)	1	0	0	0	1	20	20	20	20	18
Disease Comparison (Cohort II)	25	0	0	0	1	16	15	15	14	14
Non-Disease Comparison (Cohort III)	14	13	4	2	11	12	12	11	11	10

9.5.1. Determination of Sample Size

Based on previous experience with the OTIS Autoimmune Diseases in Pregnancy Project, we estimate that subjects will be an average of 7-10 weeks post-LMP at the time of enrollment. Given this mean gestational timing at enrollment, the anticipated spontaneous abortion and stillbirth rate is 10%, the estimated elective abortion rate is 10%, the estimated lost-to-follow-up rate is 5% (based on previous OTIS experience) resulting in approximately 75 live born infants in each group at the end of recruitment. Experience with the current OTIS Autoimmune Diseases in Pregnancy Project has demonstrated a yield of approximately 80% live born infants from the total proportion enrolled; therefore the estimated yield of 75% in this proposal is conservative. We estimate baseline rates of major

structural defects, spontaneous abortion, premature delivery, and small for gestational age (SGA) and the standard deviation for mean birth weight of full-term infants based on previous OTIS studies and on general population data. With this sample size, at 80% power, alpha of 0.05, two-tailed tests of significance (except as noted for pattern of minor anomalies), and each comparison group independently compared to the exposed group, the following minimum effect sizes will be detectable:

Table 4. Sample Size and Power for a Specified Effect Size

Endpoint	N in Each Group	Baseline Rate	RR Detectable	Power*
Major Structural Defects**	75	3%	5.5 (6.1)	80% (84%)
Specific Pattern of 3 or more minor structural defects	75	1%	10.0	71%***
Spontaneous Abortion	85	10%	2.7 (3.0)	80% (88%)
Premature Delivery	75	10% (6%)	2.8 (4.0)	80% (85%)
Small for Gestational Age	75	10% (7%)	2.8 (3.5)	80%

*based on Fishers Exact Test, 2 tailed, alpha 0.05, except for specific pattern of three or more minor anomalies as noted below; normal approximation using Open Epi software.
**primary endpoint.
***based on one-tailed Fishers Exact Test, alpha 0.05; power = 92% if two comparison groups are combined for n = 150.

The primary comparison group for all analyses will be the disease-matched tofacitinib- unexposed comparison group, consisting of two different populations: a) women with a disease for which tofacitinib has an approved indication, who have not taken tofacitinib, but who have been exposed to bDMARDS in pregnancy, including anti-TNF, (primary subgroup), AND b) women with a tofacitinib approved indicated disease who have not taken tofacitinib, and have also not been exposed to bDMARDs in pregnancy. Based on prior experience, it is expected that group "a" will almost exclusively comprise the sample, and that the power calculations shown in Table 4 are appropriate for comparison of tofacitinib exposed pregnancy outcomes to anti-TNF exposed comparison outcomes. To the extent that there are not differences between the disease-matched and healthy comparison groups, these can be combined; however, it is expected that there will be differences in selected endpoints such as preterm delivery and reduced birth size in the disease-matched group compared to healthy pregnancies.

The baseline prevalence of a specific pattern of three or more minor structural defects is estimated to be essentially zero as the occurrence of the same three low baseline frequency minor structural defects in any two children in a sample of 75 would be an extremely unlikely random event. However, for purposes of the power calculation, a hypothetical baseline prevalence estimate of 1% has been used. The relative risk detectable with this sample size (10.0) is based on approximately 71% power, and an alpha of 0.05 using a one-tailed Fishers Exact Test and 92% power to detect the same effect size if the two comparison groups demonstrate sufficiently similar baseline characteristics such that the groups can be combined. This represents a 10% birth prevalence of a specific pattern (ie, approximately seven children in the exposed sample), which is comparable to the birth prevalence of a specific pattern in other known human teratogens of moderate risk such as the anticonvulsant medications.

9.6. Data Management

Data will be collected using maternal interview, medical record, diary, and physical examination forms. Maternal interview data will be recorded on hard copies of forms, and these forms will be retained by OTIS. These forms are considered the primary data sources for the study. Medical records and medical record abstraction forms will be hard copies or electronic copies and will be retained on a secure server. Data from maternal interview and medical record abstraction forms will be extracted and entered into a customized OTIS study database located in the Research Center and developed specifically for the OTIS Autoimmune Diseases in Pregnancy Project.

The database itself has built in range limits for key variables that prevent certain data entry errors. In addition, all data entry forms will be reviewed for logical errors by the study data manager on a bi-monthly basis, and 100% of key variables are double-checked for data entry accuracy. The study statistician will also conduct reviews of the cumulative data from the study in the database for distributions and values that are illogical. The study manager will be responsible for working with the data manager and the supervisory staff to oversee the data validation procedures.

Access to the database will be controlled by password, with different access privileges assigned to the managers, interviewers and data entry staff, and administrative staff; these privileges are outlined in detail in the OTIS Data Management Guide (DMP), Data Entry Standard Operating Procedure (SOP), and supplements to these guides. An audit log is built into the database to archive all such entry edits. Hard copies of participant files and subject signed consent forms will be kept in a locked cabinets, in locked file rooms, under the supervision of the study investigators. Data collection and validation procedures will be detailed in appropriate operational documents.

9.6.1. Case Report Forms (CRFs)/Data Collection Tools (DCTs)/Electronic Data Record

As used in this protocol, the term CRF should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study.

A DCT is required and should be completed for each included patient. The completed original DCTs are the sole property of the OTIS Research Center and should not be made available in any form to third parties, except for appropriate regulatory authorities, without written permission from the Principal Investigator. The OTIS Research Center shall ensure that the DCTs are securely stored at the the OTIS Research Center in paper form and will be secured in a locked room *t*o prevent access by unauthorized parties.

The OTIS Research Center has ultimate responsibility for the collection and reporting of data agreed to in the protocol, and entered on the *DCTs* and any other data collection forms (source documents) and ensuring that they are accurate, authentic/original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. The *DCTs* must be initialed by an authorized staff member to attest that the data contained on the *DCTs* are true. Any corrections to entries made in the *DCTs* or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

Information in the medical records must match data collected on the DCTs (abstraction forms).

9.6.2. Record Retention

To enable evaluations and/or inspections/audits from regulatory authorities, the investigator agrees to keep all study-related records, including the identity of all participating patients, all original signed informed consent/assent documents, copies of all DCTs, safety reporting forms, source documents, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports. The records should be retained by the OTIS Research Center according to local regulations or as specified in the research agreement, whichever is longer. The OTIS Research Center must ensure that the records continue to be stored securely for so long as they are retained.

If The OTIS Research Center becomes unable for any reason to continue to retain study records for the required period, Pfizer should be prospectively notified. The study records must be transferred to a designee acceptable to Pfizer.

Study records must be kept for a minimum of 15 years after completion or discontinuation of the study, unless the investigator and Pfizer have expressly agreed to a different period of retention via a separate written agreement. Record must be retained for longer than 15 years if required by applicable local regulations.

The OTIS Research Center must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

9.6.3. Data Handling Conventions for the OTIS Pregnancy Registry

Initial identification of major structural defects is performed by the study Data Coordinator, and then verified and classified by the Study Manager using the CDC coding manual. Final validation of the classification of all major birth defects reported in the study will be conducted by the OTIS Co-Investigator with expertise in the diagnosis of birth defects. All

prenatal exposures to medications and vaccines are coded using the Slone Drug Dictionary (http://sites.bu.edu/slone-drug-dictionary/).

Twins or higher order multiples are handled as one pregnancy outcome. For example, if the pregnancy ends in at least one live born infant, the outcome is considered a live born outcome. If either or both twins have a major birth defect, the outcome is considered one major birth defect outcome. Twins are excluded from analyses of preterm delivery, small for gestational age infants, and postnatal growth.

Lost-to-follow-up status is designated if a participant withdraws from the study before the outcome of pregnancy is known or reported, or if study staff are unable to make contact with the study participant within 12 months of the estimated end of pregnancy in order to obtain outcome information. Before a subject is designated as lost to follow up, the subject or reporter receives at least 13 telephone attempted contacts by phone, email, written correspondence; and alternative contact information that is requested upon enrollment is utilized, as well. All follow-up attempts are documented. Participants who are lost-to-follow-up but who have at least one day of follow-up after enrollment are included in time-to-event outcomes such as spontaneous abortion if they are otherwise eligible for inclusion in that analysis. The current OTIS Autoimmune Diseases in Pregnancy Project has experienced extremely low losses to follow-up (<5% of enrolled subjects) by virtue of maintaining consistent contact with the pregnant woman. Losses to follow up are summarized in the Registry Interim and Final Reports.

Any study participant may withdraw from the study at any time for any reason; however, data that have been collected up to the time of withdrawal may be used. Women who withdraw from the study after the collection of birth outcome will not be considered lost-to-follow-up. Women who withdraw from the study prior to the collection of birth outcome will be considered lost-to-follow-up and the statistical analysis plan addresses the method whereby these data will be reported.

Duplicate reporting is possible. However, because participant identifiers are collected for this study, any duplicate report should be readily recognized. At times a report of a pregnancy exposure may come to the Registry from more than one source, eg, the Sponsor, a physician, as well as the pregnant woman. The identification of duplicate reports is conducted by routinely reviewing the database. Duplicate reports will be identified through participant identifiers and by comparing exposure, outcome, event dates and descriptions if the participant identifiers are not available from both sources. If a duplicate is identified through a systematic check for duplicates, the case reported earliest or the one with the most complete data is maintained as the valid case and updated with any data from the other report not already captured.

The primary source for information collected on demographics and exposures is by maternal interview, as the participant typically provides more accurate information than the medical records, especially in regards to non-prescription medications and any medications not taken as prescribed. Doses, dates, and timing of exposure are confirmed with medical records. If the medication is administered in the office, the medical record is the primary source; if the

medication is administered at home and there is a discrepancy between the record and maternal report, the participant is contacted and asked about the discrepancy.

The medical record is the primary source for type of prenatal test, date, and results of prenatal tests, disease diagnosis, and infant outcomes, including birth and postnatal growth, and major structural defects.

Data included in the interim annual reports is cumulative, therefore data may change when additional information is received either by maternal report or by medical records.

The method and duration of storage of data is addressed in the informed consent. Access to the database will be controlled by password. Hardcopies of participant files, original oral consent signed and dated by the interviewer, signed consent forms, and original signed medical record release forms will be kept in a locked file room, in locked cabinets, and scanned into an electronic file, under the supervision of the OTIS Research Center.

Missing values for the critical data for OTIS studies are typically very few and nearly always less than 10%. There is generally no need to include imputation strategies; however, depending on the prevalence of missingness, sensitivity analyses will be conducted. These will be specified in the SAP.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

The primary population for analysis will be those enrolled in the prospective cohort study (see Section 9.2.1). Statistical analyses of those enrolled outside the cohort study (see Section 9.2.4) will be descriptive only. These cases constitute an exposure case series, so tables of pregnancy characteristics, exposures and outcomes will be included in the interim and annual reports, and tabulations of the frequencies of events will be included by category of report: retrospective vs. prospective, reasons for exclusion, timing of exposure, and indication for use of the medication.

Demographic and baseline characteristics will be compared between groups. Discrete variables will be compared between groups using chi-square tests or Fishers Exact test as appropriate.

The primary analysis for the cohort study will be a comparison of the prevalence of major structural defects in live born infants between the tofacitinib-exposed group and the primary Comparison Group I (see Section 9.2.2 and 9.2.3). Comparison between each of the groups will be carried out using chi-squared or Fisher's exact tests. A point estimate of the crude (ie, unadjusted) risk ratio (RR) of the exposed group versus the comparison group, as well as its 95% confidence interval (CI) will be computed. When the expected frequency of any of

the cells of the contingency table is less than five, the CI will be obtained by an exact method using the software StatXact. Due to the observational nature of the study, the above crude estimate of RR will be further adjusted for confounders summarized in a propensity score (PS) to obtain the estimated causal risk ratio. The primary analysis of the primary endpoint will be conducted at the end of the study. It is unknown to what extent pregnancies with the combination of tofacitinib and methotrexate exposure will enroll in the cohort study; however, to the extent that this occurs, the disease-matched comparison group will incorporate a similar number of pregnant women with methotrexate exposure with or without concomitant exposure to any other systemic therapies.[18]

Table 5. Denominators by Outcome

Outcome	Denominator
Major Structural Birth Defects Among Live Births	Within each cohort the denominator is the number of cohort-eligible pregnancies ending in live birth. At least one malformed infant in an individual pregnancy is considered one malformed outcome in all cohorts.
Major Structural Birth Defects Among All Pregnancies	Within each cohort the denominator is cohort eligible pregnancies with any outcome excluding those lost-to-follow- up. At least one malformed fetus/infant in an individual pregnancy is considered one malformed outcome in all groups.
Spontaneous Abortion	Pregnancies enrolled in the study prior to 20.0 weeks' gestation with at least 1 follow-up data collection point after enrollment date. Exposure can occur any time in pregnancy prior to the event.
Preterm Delivery	Pregnancies enrolled prior to 37.0 weeks' gestation and ending in at least one live born infant. Excludes twins or higher order multiples due to inherent higher risk of preterm birth in multiples. Exposure can occur any time in pregnancy prior to the event.
Small for Gestational Age Infants	Pregnancies ending in at least one live born infant; excluding twins or higher order multiples due to the inherent higher risk of reduced birth size in multiples. Exposure can occur any time in pregnancy prior to the event.
Stillbirth	All pregnancies, excluding lost-to-follow-up. Exposure can occur any time in pregnancy prior to the event.
Elective Termination	All pregnancies, excluding lost-to-follow-up. Exposure can occur anytime in pregnancy prior to the event.

Outcome	Denominator
Postnatal Growth	Pregnancies ending in at least one live born infant with pediatric growth records available at approximately 1 year of age. Multiples are excluded. Exposure can occur anytime in pregnancy.

Indication-specific analyses will also be conducted pending sufficient sample size. The sample size for the study is projected to be 300 participants for all indications and all cohort groups. However, if the sample size is met prior to the recruitment end date in the contract, recruitment will continue during the allotted recruitment period to allow for 300 participants per indication and cohort group. Only descriptive analyses will be presented if achieved sample size does not allow for analytic comparisons. The study may be terminated at any time based on these findings. This decision will be considered by OTIS and the Sponsor, and a recommendation made upon review by the Advisory Committee.

- External comparisons:
  - The overall rate/proportion of major structural defects can be compared to the most recently available rate/proportion from the MACDP.
- The evaluation for a pattern of defects will be conducted using the following steps:
  - A review of major structural defects will be made by category (as outlined in Section 9.4.6). A review of specific malformations will be conducted taking into consideration timing, dose, and biological plausibility.
  - Structural defects identified in aborted fetuses will be reviewed separately from the primary analysis. Pregnancy outcome in subjects who did not meet the study qualifying criteria (ie, prior prenatal diagnosis of fetal abnormality, late gestational age, or retrospective cases) will also be reviewed separately.
  - A comparison among groups of the proportion of infants with any three or more minor structural defects will be made without regard to pattern.
- Among infants with three or more minor defects, the tofacitinib-exposed group will be examined for evidence of a specific pattern of three or more defects in any two or more children. If such a pattern is identified, Control Groups I and II will be evaluated for any evidence of the same pattern.
- Inter-rater reliability:
  - There may be variability in the assessment of minor structural defects among the study dysmorphologists. This possibility will be addressed in three ways:

The participating dysmorphologists have been working with this study protocol in the existing OTIS Autoimmune Diseases in Pregnancy Project and have participated in group training and evaluation exercises. These reliability evaluations involve having examiners independently examine the same infant and comparisons of exam results and measurements are made. These evaluation exercises will continue periodically throughout the duration of this Registry.

If a pattern of minor structural defects is identified in the interim or final analysis of the study data, photographs of the infants exhibiting this pattern will be independently evaluated by other examiners, and if deemed necessary, affected children can be re-examined by one of the other dysmorphologists to ensure agreement.

In previous studies involving the evaluation of minor structural defects, certain minor structural defects tended to be less reliably detected than others. This raises the possibility of missed identification of a pattern that includes one or more of those defects. If the interim or final analysis suggest that one or two minor defects occur substantially more frequently among exposed infants regardless of examiner, and among these children an additional defect or defects has been identified only by certain examiners, it may be necessary to have infants with those defects re-examined by a one of the other dysmorphologists.

9.8. Quality Control

Data used in this study are secondary use of data collected as part of the existing OTIS registry, which has established quality control practices. Interview, and examination data will be recorded on hard copies of forms, and medical records and medical record abstraction forms will be electronic or hard copies of forms. These records and forms will be retained at the Research Center. Data from these forms will be extracted and entered into a customized database located at the Research Center. The data will be extracted and entered by trained study personnel with extensive experience with this type of information. Entries will be periodically reviewed for logical errors, and a random subset of intake and outcome forms will be double-checked for data entry accuracy. The method and duration of storage of data is addressed in the informed consent, that each subject will agree to in order to receive medical record information. All records are maintained for a minimum of 10 years following study completion.

Access to the database will be controlled by password. Hard copies of participant files and subject signed consent forms will be kept in a locked cabinet under the supervision of the study investigators.

The data will be entered by trained study personnel with extensive experience with this type of information. Data will be collected and entered into the database according to the SOPs for data collection and data entry established for this study.

The data manager will calculate monthly error rates for each data entry staff person and for the study overall, and will recommend and initiate training/retraining where quality standards are not being met. The study manager will oversee this process and verify that training standards are achieved.

For the primary study endpoint of major structural defects, verification of the outcome identified and classification is performed on a monthly basis is provided by blinded review by co-investigator, Kenneth Lyons Jones, MD.

9.9. Limitations of the Research Methods

The primary limitation of a cohort study utilizing volunteer subjects is potential selection bias. The use of comparably selected controls in both groups will address this concern to some extent. However, women who agree to enroll in the cohort study may represent particularly high or low risk pregnancies.[19] The study results will therefore be strictly generalizable to women fitting the profile of the sample of women who enroll. Over 5 years of the original RA study, only two tofacitinib-exposed patients in the "cohort analysis" group were recruited. Due to this, several measures including expanded marketing and promotional materials and targets have been taken to help ensure eligible patients are referred to OTIS.

Another limitation of the study design relates to the evaluation of spontaneous abortion rates. Rates of early spontaneous abortion, ie, at 7-9 weeks post-LMP or less, will not be measured in a study that enrolls women after recognition of pregnancy. The study results with respect to spontaneous abortion will be limited to relative risk for late first-trimester and early second-trimester pregnancy loss.

Because early prenatal testing is so prevalent in the U.S. and Canada, it may be difficult to achieve adequate numbers of participants if all pregnancies with prior prenatal testing are excluded from the analysis. Therefore, the Registry will include pregnancies enrolled prior to outcome but after a prenatal test has been performed as long as the test does not indicate the presence of a major structural defect. The FDA guidance document[20] acknowledges that such an approach may be necessary to accrue adequate numbers. However, this practice could potentially bias the results by lowering the overall estimate of the prevalence of major structural defects.[21] The data analysis will address this by stratifying on use of prenatal testing and on gestational timing of enrollment.

The calculation of frequency of major structural defects excludes fetal losses (spontaneous abortions, induced abortions, or fetal deaths) for which no major structural defects have been detected as they may introduce a classification bias. It is unknown what percentage of these pregnancies consists of potentially normal outcomes or pregnancies with major structural defects. The Registry attempts to obtain information on major structural defects detected at the time of the outcome. However, the malformation status of the aborted fetus may not be known. For this reason, the primary comparison for the primary endpoint of the study will be conducted among pregnancies ending in live birth, and a secondary analysis of the primary endpoint will include all pregnancies with known outcome.

It is expected that many exposures to tofacitinib will occur in unintended pregnancies. Although more than half of all pregnancies in the U.S. are unintended,[22] the possibility of confounding by age, race, and other demographic variables will be considered. For example, the rate of unintended pregnancies is higher among low-income women/families than among the other socioeconomic groups. It is possible that demographic variables will be associated with treatment as well. As such, these factors will be taken into consideration in the recruitment of comparison groups and in the analysis.

Another factor to be considered in a study anticipated to encompass a five to ten-year recruitment period is the potential impact of changing trends in prescribing practices along with physician and maternal attitudes toward the use of tofacitinib in pregnancy. The sample size is based on estimates that may require revision as the study progresses. In addition, as more post-marketing experience with the medication is accumulated, the number and characteristics of exposed pregnancies, the proportion electively terminated, and the length of exposure may change. These trends will need to be addressed in the analysis.

The study design has strengths with respect to the control of a large number of potential confounders. Information will be collected repeatedly throughout pregnancy on a variety of factors which may be related to exposure and to pregnancy outcome, and the use of a disease-matched comparison group can aid in addressing confounding by indication. Misclassification bias due to poor recall is thought to be reduced in prospective study designs such as this, as each subject is interviewed at several predetermined intervals during pregnancy. Misclassification bias in outcome is minimized in this study design through the use of a specialized physical examination and a standardized evaluation protocol. Another strength of the study design is the anticipated minimal lost-to-follow-up rate. Based on previous experience of the investigators in the OTIS Autoimmune Diseases in Pregnancy Project and other similar studies, and the frequent subject contact, lost-to-follow-up is expected to be <5%, and therefore not expected to pose a threat to the validity of study results.

Finally, despite the small sample size, one of the strengths of this study is the capacity to investigate the possibility of minor anomalies via physical examination by trained experts. Although clusters of such malformations are rare, evaluations of patterns have been used with success to detect moderate level teratogens (eg, anticonvulsants).

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

10.1. Patient Information

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

Patient personal data will be stored at the OTIS Research Center in paper form and will be secured in a locked room to ensure that only authorized study staff have access. Medical records will be stored electronically on secure servers that are password protected. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site shall be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when selected study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to authorized parties will be identified by this single, patient-specific code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the clinical study agreement and applicable privacy laws.

10.2. Patient Consent

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of patient personal data. Such measures will include omitting patient names or other directly identifiable data in any reports, publications, or other disclosures, except where required by applicable laws.

To protect the rights and freedoms of natural persons with regard to the processing of personal data, when study data are compiled for transfer to Pfizer and other authorized parties, any patient names will be removed and will be replaced by a single, specific, numerical code. All other identifiable data transferred to Pfizer or other authorized parties will be identified by this single, patient-specific code. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patients' personal data consistent with the vendor contract and applicable privacy laws.

10.3. Patient Withdrawl

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral,or administrative reasons. In any circumstance, every effort should be made to documentsubject outcome, if possible. The investigator should inquire about the reason for withdrawaland follow-up with the subject regarding any unresolved adverse events. If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

10.4. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to Pfizer.

This protocol and informed consent documents have been approved by the Institutional Review Board (IRB) at the University of California, San Diego. The chairman or the recording secretary of the IRB have signed a form indicating approval. Notification of the Board's approval of the study was provided to the Sponsors prior to initiation of the Registry.

10.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in International Society for Pharmacoepidemiology's Guidelines for Good Epidemiology Practices for Drug, Device, and Vaccine Research in the United States , US FDA regulatory requirements, in accordance with the ethical principles of the Declaration of Helsinki (1995), and the HIPAA (Health Insurance Portability and Accountability Act).[23,24,25]

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the MedWatch Report Form are as follows:

- All serious and non-serious AEs with explicit attribution to **Pfizer drug** that appear in the reviewed information must be recorded on the Interview Form and reported, within 24 hours of awareness, to Pfizer Safety using the MedWatch Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the MedWatch Report Form.

For these AEs with an explicit attribution involving exposure to a Pfizer product, the safety information identified in the unstructured data reviewed is summarized in the Event Narrative section of the report form. No follow-up on related AEs will be conducted.

All research staff members must complete the following Pfizer training requirements:

- "YRR Training for Vendors Working on Pfizer Studies (excluding interventional clinical studies and non-interventional primary data collection studies with sites/investigators)".

These trainings must be completed by research staff members prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

Re-training must be completed on an annual basis using the most current Your Reporting Responsibilities training materials.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report describing the study endpoints will be prepared by the OTIS Research Center and provided to the tofacitinib clinical program teams. The Sponsor will communicate the results to the FDA and the EMA, and as requested by other relevant regulatory authorities. Conference abstracts and manuscripts based on specific endpoints of interest may be developed for external publication purposes. A final report will be disclosed on the EU PAS register.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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14. LIST OF TABLES

15. LIST OF FIGURES

Not Applicable.

ANNEX 1. LIST OF SERIOUS OPPORTUNISTIC INFECTIONS UP THROUGH ONE YEAR INFANT FOLLOW-UP

Tuberculosis
X-ray proven pneumonia (requiring antibiotic treatment and/or hospitalization)
Neonatal sepsis
Meningitis (asceptic or culture proven)
Bacteremia
Invasive fungal infection (biopsy proven)
Pneumocystis
Septic arthritis
Osteomyelitis
Abcess (deep tissue)

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not Applicable.

ANNEX 3. ADDITIONAL INFORMATION

Not Applicable.

Document Approval Record

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Non-Interventional Study Protocol
A3921203

Tofacitinib Pregnancy Exposure Registry OTIS Autoimmune Diseases in Pregnancy Project Statistical Analysis Plan (SAP)

Version: 1.0

Author: Prof. Ronghui (Lily) Xu, Yunjun (Jennifer) Luo (Department of Pediatrics, Division of Environmental Science & Health, UC San Diego)

Date: 08-17-2023

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Not applicable

2 INTRODUCTION

Note: in this document, any text taken directly from the study protocol is ***italicised***.

Tofacitinib is an oral janus kinase (JAK) inhibitor and is currently approved in the US for adults with moderately to severely active RA, active PsA, or active ankylosing spondylitis who have had an inadequate response to or intolerance to one or more TNF blockers. It is also approved for the treatment of adults with moderate to severely active UC who have had an inadequate response to or intolerance to one or more TNF blockers, as well as approved for the treatment of polyarticular course juvenile idiopathic arthritis (pcJIA) in patients 2 years of age and older who have had an inadequate response to or intolerance to one or more TNF blockers. *Human pregnancy exposure data for tofacitinib is limited; however, tofacitinib is likely to be utilized by pregnant women when they and their doctors believe that risk/benefit considerations favor its use. Also, given the frequency of unplanned pregnancies, information regarding the safety of tofacitinib in human pregnancy is essential from a public health perspective.*

This non-interventional study is designated as a Post-Authorization Safety Study (PASS) and is a post-marketing commitment to the Food and Drug Administration (FDA).

2.1 Study Design

This is a prospective, observational, exposure cohort study of pregnancy and infant outcomes in women with a disease for which tofacitinib has an approved indication and enrolled in the registry prior to 20 weeks gestation, i.e., the number of weeks *from the first day of the last menstrual period (LMP). The birth prevalence or incidence of outcomes* (defined in Sections 4.2 and 4.3) will be described for women exposed to tofacitinib within the first trimester and *those observed in 2 unexposed comparator groups: a disease-matched comparison group of women who have not used tofacitinib during pregnancy (disease comparison group), and a comparison group of healthy women who do not have an autoimmune disease, have not had exposure to a known human teratogen, and have not taken tofacitinib in pregnancy (healthy comparison group).*

The study was originally planned for five years. In 2019, the protocol was amended to include any approved indication, and the data collection timeline was extended for an additional five years, with a final study report and analysis projected for March 2024.

Study Population

The study population includes pregnant women who reside in the U.S. or Canada, who do or do not have a disease for which tofacitinib has an approved indication, and have or have not used tofacitinib for any length of time in pregnancy.

Three groups of participants will be enrolled in the study cohort prior to 20 weeks gestation and followed for pregnancy and infant outcomes:

- *Pregnant women with an approved indication for tofacitinib who are exposed to tofacitinib within the first* trimester.
- *Pregnant women with an approved indication for tofacitinib but who are not exposed to tofacitinib during pregnancy;*
- *Pregnant women who do not have an autoimmune disease, have not had exposure to a known human teratogen, and have not taken tofacitinib during pregnancy.*

Another group of participants who are tofacitinib-exposed but do not meet cohort study selection criteria will be excluded from the cohort analysis, but enrolled in the exposure series as information on their birth outcomes can be useful for hypothesis generating when reviewing the cohort data.

Data source

Data will be collected using maternal interviews, medical records (obstetric, delivery hospital, pediatric, rheumatologist, dermatologist, gastroenterologist, and/or other specialty provider), and pregnancy exposure diary. Maternal interview data will be recorded on hard copy forms, and medical record abstraction data will be recorded on electronic forms, which will be retained by OTIS. Maternal interview forms are considered the primary data sources for the study. Data from these forms will be extracted and entered into a customized OTIS study database located at the OTIS Research Center and developed specifically for the OTIS studies.

Study Size

The target sample size for the study is 300 pregnant women; 100 pregnant women in each of the three cohort groups: tofacitinib-exposed, disease-matched unexposed, and non-diseased unexposed.

2.2 Study Objectives

The objectives of the Tofacitinib Pregnancy Exposure Registry are to:

- *Monitor planned and unplanned pregnancies exposed to tofacitinib.*
- *To evaluate the potential teratogenic effect of this medication relative to the primary pregnancy outcome of major structural birth defects, specifically a pattern of anomalies, and the secondary pregnancy outcomes of spontaneous abortion,*

stillbirth, elective termination, *preterm delivery, small for gestational age, small for age for postnatal growth of live born children to one year of age, serious or opportunistic infections or malignancies in live born children up to one year of age.*

- *To describe pregnancy outcomes of all tofacitinib-exposed pregnancies enrolled in the exposure series (those not eligible for the tofacitinib-exposed cohort).*

3 ANALYSIS SETS/POPULATIONS

The analysis sets/populations are described below.

3.1 Inclusion Criteria for "Cohort Analysis" Group

The study will enroll women in three cohorts:

1. *Tofacitinib-Exposed Group- Inclusion Criteria.*

   - *Currently pregnant women who have had an exposure to tofacitinib, for the treatment of a disease for which tofacitinib has an approved indication, for any number of days, at any dose, and at any time from the 1st day of the last menstrual period up to* the end of the 1st trimester. *If the date of LMP is unclear, or if a first-trimester ultrasound has been done and the estimated date of conception is more than one week discrepant from the menstrual period calculation, the first-trimester ultrasound-derived date will be used to calculate a date for LMP and conception, and*

   - *Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and*

   - *Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.*

2. *Comparison Group I: Disease-matched Unexposed (to tofacitinib) Cohort – Inclusion Criteria.*

   - *Currently pregnant women with a diagnosis of a disease for which tofacitinib has an approved indication, by maternal report and validated by medical records, who have not taken tofacitinib any time since first day of last LMP to delivery in the current pregnancy but who may or may not have taken another medication for their disease including an anti-TNF or other biologic in the current pregnancy. To the extent that tofacitinib-exposed women enrolled in the cohort study also have methotrexate exposure, women in the disease-matched unexposed comparison group I with*

methotrexate exposure will be recruited to frequency match the number with tofacitinib plus methotrexate, and

- *Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and*

- *Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.*

3. *Comparison Group II: Non-diseased Unexposed (to tofacitinib) Cohort -Inclusion Criteria.*

    - *Currently pregnant women who have not had exposure to a known human teratogen or biologic agent as confirmed by the OTIS Research Center, and*

    - *Currently pregnant women who do not have an autoimmune disease*

    - *Currently pregnant women who agree to enroll prior to 20 weeks' gestation, and who have not had prenatal diagnosis of any major structural defect prior to enrollment, and*

    - *Currently pregnant women, who agree to the conditions and requirements of the study including the interview schedule, release of medical records, and the physical examination of live born infants.*

3.2 Exclusion Criteria for "Cohort Analysis" Group

Patients meeting any of the following criteria will not be included in the analytic component of the study:

1. *Tofacitinib-Exposed Group-Exclusion Criteria.*

    - *Currently pregnant women who have had an exposure to tofacitinib during pregnancy but have also had an exposure to one or more of the known human teratogens or medications of unknown safety used for the same indication during the index pregnancy* (meaning the pregnancy with which the participant is enrolled in the cohort study. Note that women can enroll only once in this cohort, and additional exposed pregnancies will be enrolled in the exposure case-series.) *will not be qualified as subjects for the tofacitinib-exposure group in the cohort study:*

        - *Chlorambucil;*
        - *Cyclophosphamide;*
        - *Mycophenylate mofetil;*
        - *Adalimumab;*

- *Abatacept;*
- *Certolizumab pegol;*
- *Etanercept;*
- *Tocilizumab;*
- *Infliximab;*
- *Golimumab;*
- *Vedolizumab;*
- *Secukinumab;*
- *Ustekinumab;*
- *Ixekizumab;*
- *Or leflunomide within one year prior to conception unless a documented blood level below the detectable limit prior to enrollment is available;*

- *Women who have first contact with the project after prenatal diagnosis of any major structural defect,*

- *Women who have enrolled in the cohort study with a previous pregnancy,*

- *Women who have used tofacitinib for an indication other than an approved indicated disease*

- *Note: Retrospective cases will be followed as part of the exposure case-series, but will not be included in the cohort study* (ie will not be part of the cohort analysis).

2. *Comparison Group I – Exclusion Criteria*

   - *Currently pregnant women who have had an exposure to the medications listed below that are known or suspected human teratogens:*

     Chlorambucil; Cyclophosphamide; mycophenylate mofetil; or leflunomide within one year prior to conception unless a documented blood level below the detectable limit prior to enrollment is available.

   - *Women who have first contact with the project after prenatal diagnosis of any major structural defect.*

   - *Women who have enrolled in the cohort with a previous pregnancy.*

3. *Comparison Group II – Exclusion Criteria*

   - *Currently pregnant women who incur an exposure to a known teratogen in the first trimester after the time of enrollment will be disqualified as subjects for purposes of the analysis.*

   - *Women who have a diagnosis of an autoimmune disease*

- *Women who have first contact with the project after prenatal diagnosis of any major structural defect,*

- *Women who have enrolled in the cohort study with a previous pregnancy.*

3.3 Tofacitinib-exposed Pregnancies not Eligible for the Cohort Study ("exposure series")

By study design, pregnancies that do not meet the exposed cohort criteria for reasons described in Sections 3.1. and 3.2 *will be invited to enroll in a separate "exposure series".*

With informed consent, data will be collected from maternal questionnaires, medical records review and the physical examination using the same protocol as the cohort study to the extent possible.

4 ENDPOINTS AND COVARIATES

Exposure will be defined as tofacitinib treatment by maternal report and verified by medical record review, with detailed information on the gestational timing, route of administration, dose, and dates of exposure. Outcome variables include major structural birth defects, spontaneous abortion, stillbirth, elective termination for any reason, preterm delivery, minor structural defect, *infant birth size, postnatal growth of live born children up to one year of age, and serious or opportunistic infections or malignancies in live born children up to one year of age. These will be obtained by maternal report and verified by medical record review.*

4.1 Baseline variables

- Maternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34);
- Paternal age (years) at due date, continuous and categorical (<25, 25-29, 30-34, >34);
- Maternal race (Caucasian/White, Black, Asian, Pacific Islander, Native American, Other);
- Maternal ethnicity (Hispanic, Non-Hispanic);
- Maternal educational category (years of completed education <12, 12-15, >15);
- Hollingshead Socioeconomic Category (1, 2, 3, 4 or 5); This is based on four-factor Hollingshead categories incorporating maternal and paternal education and occupation; highest socioeconomic status category = 1; lowest socioeconomic status category = 5
- Family income category (<$10,000, $10,000 - <$50,000, ≥$50,000)
- Maternal height (cm);
- Maternal Pre-pregnancy body weight (kg);
- Maternal pre-pregnancy BMI (kg/m^2) (<18.5, 18.5- <25, 25- <30, >=30);
- Number of times ever pregnant, including current pregnancy (1, 2-3, 4-5, >=6);
- Number of previous live birth or stillbirth deliveries (0, 1-2, 3-4, >=5);

- Number of previous pregnancies ending in spontaneous abortion (0, 1, 2, >=3);
- Number of previous pregnancies ending in elective termination (0, 1, 2, >=3);
- Gestational age (weeks from the first date of LMP) of pregnancy at time of enrollment, continuous and categorical (<=13, >13 - <20);
- Referral source (OTIS service, HCP, Internet, Sponsor, Other);
- Maternal geographic area of residence (U.S., Canada);
- Year of diagnosis with the study indications (Cohort 1 and Cohort 2 only);
- Year of enrollment;
- Comorbidities (e.g. depression and anxiety, other autoimmune conditions);
- Prenatal, multivitamin or folic acid supplement use by timing (began prior to conception, post-conception only, not taken at all);
- Any alcohol use during pregnancy (yes/no); if the quantity and frequency of exposure meets the definition of human teratogen, this exposure would also be classified under the bullet "Maternal exposure to another known human teratogen"
- Tobacco use (ie use of any tobacco product) during pregnancy (yes/no);
- Any caffeine use during pregnancy (yes/no);
- Prenatal diagnostic tests performed prior to enrollment (ultrasound level 1, ultrasound level 2, chorionic villus sampling, amniocentesis) (yes/no);
- Prenatal diagnostic tests performed anytime in pregnancy (ultrasound level 1, ultrasound level 2, chorionic villus sampling, amniocentesis) (yes/no);
- Intended/unintended pregnancy (yes/no);
- In Vitro Fertilization (IVF) (yes/no);
- Previous child with major structural defect (yes/no);
- Previous preterm delivery (yes/no);
- Maternal pregnancy exposure to another known human teratogen (e.g. methotrexate) (yes/no);
- Exposure to other medications and/or historical exposure to medications such as steroids during pregnancy (yes/no);
- Disease severity scores of the study indications (Cohort 1 and Cohort 2 only), collected at each interview during pregnancy.

Due date and gestational age are calculated based on the following criteria: If a woman has a regular 28-day menstrual cycle and the woman knows the first date of her LMP, the due date is 40 weeks from the first date of her LMP. If the date of the LMP is unclear, or if a first-trimester ultrasound has been done and the estimated date of conception (EDC) from the ultrasound is more than one week discrepant from the menstrual period calculation (i.e. 2 weeks after first date of LMP), the first-trimester ultrasound-derived date will be used for the dates of LMP, conception and due date. If the date of the LMP is unclear and a first trimester ultrasound is not available, and a second trimester estimated date of conception is more than 14 days discrepant from the menstrual period calculation, the second-trimester ultrasound-derived date will be used for the dates of LMP, conception and due date. If the date of the LMP is unclear and a first or second trimester ultrasound is not available, and a

third trimester estimated date of conception is more than 21 days discrepant from the menstrual period calculation, the third-trimester ultrasound-derived date will be used for the dates of LMP, conception and due date.

4.2 Primary endpoint

The primary endpoint will be the rate of major structural defects among live born infants. In addition, the rate of major structural defects will be computed among all pregnancies excluding lost-to-follow up. A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.

A major structural birth defect is defined as a defect that has either cosmetic or functional significance to the child (e.g., a cleft lip) and is identified up to 1 year of age by the mother, the health care provider/medical record, or identified in the dysmorphological examination. Major defects are classified according to the Centers for Disease Control and Prevention (CDC)'s Metropolitan Atlanta Congenital Defects Program (MACDP) coding manual for major structural defects [1]. The MACDP is a population-based birth defects monitoring program for metropolitan Atlanta in the state of Georgia in the US, and involves ascertainment and classification of birth defects identified at delivery or postnatally with re-hospitalization up through 6 years of age.

4.3 Secondary endpoints

Pregnancy Outcomes

Spontaneous abortion (SAB) is defined as non-deliberate embryonic or fetal death that occurs < 20.0 weeks' gestation post-LMP. This applies to women in all three cohorts who are enrolled in the study prior to 20.0 weeks' gestation, and only to those in Cohort 1 who are enrolled and exposed prior to 20.0 weeks' gestation. In pregnancies involving multiples with one or more of the outcomes ending in SAB, when there are no live births, the pregnancy is counted as one SAB event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.

Stillbirth is defined as a non-deliberate fetal death that occurs at or after 20.0 weeks' gestation but prior to delivery. In pregnancies involving multiples with one or more of the outcomes ending in stillbirth, when there are no live births, the pregnancy is counted as one stillbirth event; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.

Elective termination is defined as deliberate interruption of pregnancy by surgical or medical means. In pregnancies involving multiples with one or more of the outcomes ending in elective termination, when there are no live births, the pregnancy is counted as one elective termination; however, when the pregnancy ends in at least one live-born infant, the pregnancy is counted as a live birth outcome.

Preterm delivery is defined as live birth prior to 37.0 weeks' gestation as counted from LMP. This applies to women in all three cohorts who are enrolled in the study prior to 37.0 weeks' gestation, and only to those in Cohort 1 who are enrolled and exposed prior to 37.0 weeks' gestation, excluding pregnancies with twins or higher order multiples.

Subjects will be considered lost-to-follow-up if they have completed the initial intake interview but subsequently fail to complete the outcome interview despite a standard number of telephone attempts and attempt to contact by mail as per study procedure manual within 1 year of the mother's estimated due date.

Infant Outcomes

The proportion of live born infants who receive the dysmorphological exam who have 3 or more minor malformations or a pattern of specific minor malformations is a secondary outcome. A minor structural defect is defined as a defect that has neither cosmetic nor functional significance to the child and as itemized on the study-related dysmorphology examination form [2]. There are two definitions for this outcome, both of which use a denominator based on the number of infants who received a dysmorphological examination. The first definition is the proportion of infants with at least 3 minor structural defects of any type. The second definition is the proportion of infants with specific patterns of at least 3 minor structural defects. Each specific pattern, if any are identified, must be observed in at least 2 infants exposed to tofacitinib. As an example, if 2 infants in Cohort 1 had the following minor structural defects: "hair pattern unruly", "prominent nasal bridge", and "clinodactyly 5th finger bilateral", this would constitute one specific pattern of minor structural defects. For each specific pattern identified in Cohort 1, infants in Cohorts 2 and 3 who have the same specific pattern(s) are selected to comprise the numerator for those cohorts. In infants who have more than one specific patterns of at least 3 minor structural defects, each specific pattern will qualify as its own endpoint; therefore, the infant would be counted more than once.

All infants from twin or higher order multiple pregnancies who received the dysmorphology examination are included in the analysis of the first definition. However, in the analysis of the second definition, only one infant from a twin or higher order multiple pregnancy can be qualified as a child with the same pattern of minor structural defects as another child, due to lack of independence for this outcome between related individuals.

Small for gestational age (SGA) is a secondary outcome. SGA is defined as birth size (weight, length or head circumference) less than or equal to the 10th percentile for sex and gestational age using National Center for Health Statistics (NCHS) pediatric growth curves for full term infants. Prenatal growth curves specific to preterm infants will be used for premature infants. Pregnancies with twins or higher order multiples will be excluded.

Small for age on postnatal growth is defined as postnatal size at approximately 1 year of age (weight, length or head circumference) less than or equal to the 10th percentile for sex and age using NCHS pediatric growth curves, and adjusted postnatal age for premature infants. Pregnancies with twins or higher order multiples will be excluded.

Serious or opportunistic infections of live born infants are defined as those listed in Appendix 1 or any others that are reported and identified in infants after birth and up to 1 year of age, for any length of time identified up to 1 year of age.

Malignancies are defined as those diagnosed and reported in an infant up to 1 year of age.

5 HANDLING OF MISSING VALUES

Missing values typically occur in less than 5% of the cases for any single covariate [3]. They are assumed to be missing at random. For the outcome of SAB, for some cases the exact date of SAB might be unknown, and instead a window for possible SAB time is available. This is known as interval censored data. An exact SAB time will be imputed by sampling uniformly from the corresponding time window. The number of imputation will be 10, i.e. 10 datasets with imputed data will be created. Each imputed dataset gives a point estimate of the SAB rate as well as its standard deviation, which will be combined across the 10 datasets to obtain the final estimate of the SAB rate and its 95% CI [4].

6 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

As recruitment into the tofacitinib-exposed cohort has been much lower than originally planned, no formal statistical analysis is considered appropriate due to the low number of recruited subjects. Therefore, the outcomes will be summarized descriptively in the final report.

6.1 Analyses of baseline characteristics

Baseline characteristics will be summarized within each group. For the interim reports, all continuous variables will be summarized using the following statistics: Mean, Standard Deviation, Median, Minimum, Maximum, 1st quartile, 3rd quartile. All categorical variables will be summarized using counts and percentages. Missing data or unknown responses will not be counted in the percentages, but will be reported separately for completeness.

6.2 Analyses of primary outcome (major structural birth defects)

For the primary endpoint of major structural birth defects, the exposure of interest is receipt of at least one dose of tofacitinib at any time from the 1st day of the LMP to the end of the first trimester. The primary outcome is major structural birth defects identified before the end of the first year of life.

The crude birth prevalence of major structural defects among pregnancies ending with at least one live birth will be calculated, with 95% CI for each cohort group estimated using the Clopper-Pearson method based on the exact binomial distribution [5]. The rate will also be calculated within each of two strata, according to whether the woman had prenatal diagnostic testing, such as level II ultrasound, amniocentesis or chorionic villus sampling, prior to enrollment in the study or not.

The *crude birth prevalence* of major structural defects and 95% CIs in each cohort will also be calculated using the same method specified above among all pregnancies excluding those that are lost-to-follow-up. The rates will be compared descriptively with the most recently published rate of major birth defects from MACDP.

Stratified descriptive analyses using the same method specified above will also be presented based on gestational age at enrollment (<=13 weeks vs. >13 - <20 weeks, depending on the distribution).

A descriptive sensitivity analysis will be performed to exclude subjects with exposure to known teratogens in Cohort 1 and Cohort 2.

Another descriptive sensitivity analysis will be performed to exclude those major structural defects thought to be of chromosomal or genetic origin.

6.3 Analyses of secondary outcomes

The secondary outcomes for the study are spontaneous abortion; stillbirth; elective termination; preterm delivery; small for gestational age (SGA = <=10^{th} centile for sex and gestational age at delivery) on birth weight, length and head circumference; postnatal growth small for age and sex (<=10^{th} centile) at approximately one year of age; and a pattern of minor structural defects among those infants who received the study-related dysmorphological physical examination.

The analysis of spontaneous abortion (SAB) is complicated by left truncation in the data, i.e., women enter the study at arbitrary times in gestation. Only those women who are enrolled prior to 20.0 weeks of gestation are eligible for the analysis of SAB. Since this enrolment window was a criterion for inclusion in the cohort study, all pregnancies in the cohort study were enrolled prior to 20.0 weeks' gestation. As enrolled women are not followed from gestational age zero, survival analysis methods will be used to handle left truncation, as well as right-censoring when a subject is lost-to-follow-up prior to 20.0 weeks' gestation. The left-truncated Fleming-Harrington estimate at 20.0 weeks' gestation will be used to estimate the *crude incidence* rate of SAB with 95% CIs in each of the cohorts [6, 7]. Stillbirths and elective terminations will be analyzed in a similar fashion, although expected numbers will be at or near zero.

Women who are enrolled prior to 37.0 weeks of gestation are eligible for the analysis of preterm delivery. As this was a criterion for inclusion in the cohort study, all pregnancies were enrolled prior to 37.0 weeks' gestation. Pregnancies ending in at least one live birth will be included in the descriptive analysis. Multiple pregnancies, which are inherently at increased risk of preterm delivery, will be excluded from this descriptive analysis. These data will be descriptively analyzed using the left-truncated Fleming-Harrington estimate at 37.0 weeks' gestation to estimate preterm delivery rates in each of the cohorts along with their 95% CIs.

Endpoints relevant to SGA at birth on weight, length and head circumference, and small for age on postnatal growth at approximately 1 year of age (+3 months) for weight, length, and head circumference, respectively are all binary endpoints. The analysis populations for these endpoints will be pregnancies ending in live born singletons, as the risk of prenatal and postnatal growth deficiency is increased in multiples. The descriptive analysis of each of these outcomes will be calculated as the rate for the outcome with 95% CI for each cohort group.

Live born infants including multiples will be included in the descriptive analyses of serious or opportunistic infections, as well as malignancies. The outcome variables thus contain likely correlated data for multiples, and the generalized estimating equations (GEE) approach will be used [8, 9]. More specifically, the point estimate for the rate for that outcome with its 95% CIs will be obtained using log-binomial link and independent working correlation (R package 'geepack' or similar R package available at the time of analysis).

Live born infants including multiples will be included in the descriptive analysis of a pattern of minor structural defects. For the analysis of a pattern of minor structural defects, the population only includes those infants who received the study-related dysmorphological examination. Although specific patterns cannot be defined within twin pairs who have the same 3 minor defects, it is possible that a pattern could be identified in one member of a twin pair and a different pattern could be identified involving the second member of a twin pair. The outcome variable thus may contain likely correlated data from repeated observations of infants born to the same participant, and the generalized estimating equations (GEE) approach will be used [8, 9]. More specifically, the point estimate for the rate for that outcome with its 95% CIs will be obtained using log-binomial link and independent working correlation (R package 'geepack' or similar R package available at the time of analysis).

6.4 Analyses of outcomes of the exposure case series group

Similar descriptive analyses for all outcomes will be conducted for the exposure case series group, i.e., those exposed pregnancies which did not meet cohort criteria. These outcomes will be described separately for those enrolled prospectively before the known outcome of pregnancy and those enrolled retrospectively. There will be no stratified or sensitivity analysis for these groups though.

7 REFERENCES

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8 APPENDIX I. CONDITIONS CONSIDERED SERIOUS OR OPPORTUNISTIC INFECTION

- Any infection resulting in hospitalization or extended hospitalization
- X-ray proven pneumonia (requiring antibiotic treatment and/or hospitalization)
- Neonatal sepsis
- Meningitis (aseptic or culture proven)
- Osteomyelitis
- Bacteremia Septic
- Arthritis Abscess (deep tissue)
- Mycobacteria infection (including but not limited to tuberculosis)
- Invasive fungal infection (biopsy proven) including histoplasmosis, coccidiomycosis, candidiasis, aspergillosis, blastomycosis
- Pneumocystis jirovecii infection
- Systemic Cytomegalie Virus, Herpes zoster, and Herpes simplex infection
- Listeria infection
- Legionella infection

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Signed By:	Date(GMT)	Signing Capacity
Zhou, Xiaofeng	28-Aug-2023 13:00:28	Administrative Approval
Wang, Wenjin	08-Sep-2023 17:54:47	Final Approval

Patient's Name_____
Mother's Name:_____
DOB:_____ **Preg ID:**_____
Date Seen:_____ **Budget:**_____

Telemedicine Dysmorph Exam Form

Version 2

Calvarium	**+**	**Eval**	**No Exam**
Bifrontal Diameter Narrow			
Frontal Bossing			
Metopic Ridge			
Metopic Suture Open			
Third Fontanel			
Large Anterior Fontanel			
Occiput Prominent			
Occiput Flat			
Hair Whorl Double			
Hair Whorl Triple			
Hair Whorl Absent			
Hair Whorl Midline			
Hair Pattern Unruly			
Frontal Upsweep			
Widow's Peak			
Depigmentary Hair Changes			
Scalp Defect			
Plagiocephaly			
Sutural Synostosis			
Other			
Face			
Supraorbital Ridges			
Prominent			
Hypoplastic			
Eyebrows			
Synophrys			
Medial Flare			
Nasal Bridge			
Flat			
Prominent			
Nostrils			
Anteverted			
Hypoplastic			
Thickened			
Philtrum			
Smooth			
Vermillion Thin			
Cupid's Bow Missing			
Facial Asymmetry			
Maxillary Hypoplasia			
Other			
Eyes			
Epicanthal Folds			
Left			
Right			
Ptosis			
Left			
Right			
Eyelashes			
Absent			
Defect			
Strabismus			
Other			

Mouth	**+**	**Eval**	**No Exam**
CLEFT LIP			
Cleft Alveolar Ridge			
CLEFT PALATE			
Micrognathia			
Prognathia			
Macroglossia			
Microglossia			
Prominent Lingual Frenuli			
Other			
Ears			
Preauricular Pit			
Left			
Right			
Preauricular Tag			
Left			
Right			
Altered Shape / Position			
Other			
Neck			
Webbed			
Short			
Broad			
Low Post Hair Line			
Hair Upsweep			
Branchial Sinus			
Other			
Chest and Abdomen			
Supernumerary Nipples			
Left			
Right			
Poland Sequence			
Pectus Excavatum			
Pectus Carinatum			
Diastasis Recti			
Umbilical Hernia			
Other			
Genitalia - Male			
Undescended Testes			
Left			
Right			
Testes in Groin			
Left			
Right			
HYPOSPADIAS *(circle one)* 1°, *2°*, *3°*			
Chordee			
EPISPADIAS			
Scotalization of Phallus			
Scrotum Shawl			
Scrotum Bifid			
Absent Median Ridge			
Micropenis			
Other			

Back	+	Eval	No Exam
Sacral Dimple			
Coccygeal Dimple			
Cutaneous Marker Midline			
Other			
Arms			
Inability to fully extend elbows			
Pterygia			
Radioulnar Synostosis			
Other			
Hands			
Clinodactyly 5th Finger			
Left			
Right			
Thumb Hypoplasia			
Left			
Right			
Fingers Tapered			
Fingers Overlapping			
Finger Tip Pads Prominent			
Fingernails			
Hypoplastic			
Hyperconvex			
Simian Crease			
Left			
Right			
Aberrant Creases Other			
Interphalangeal Creases Absent			
Left PIP: 2_3_4_5_			
Left DIP: 2_3_4_5_			
Right PIP: 2_3_4_5_			
Right DIP: 2_3_4_5_			
IP Creases Extra			
Fingers			
Left			
Right			
Thenar Crease Absent			
Left			
Right			
POLYDACTYLY			
Syndactyly			
Other			
Legs			
Genu Valgum			
Patella Absent			
Other			

Feet	+	Eval	No Exam
Space increase 1-2 toes			
Left			
Right			
Syndactyly 2-3			
Left			
Right			
Toes Overlapping 5th over 4th			
Left			
Right			
Toes Overlapping – Other			
Left			
Right			
Toenails Hypoplastic			
Heels Prominent			
Left			
Right			
Vertical Sole Crease			
Left			
Right			
Metatarsus adductus			
Left			
Right			
Calcaneovalgus			
Left			
Right			
POLYDACTYLY			
Other			
Skin			
Capillary Hemangioma (count only if ≥ 1.5 cm) || Size: _____ *Location:			
Vascular Malformation			
Glabella | Size:			
Neck | Size:			
Eye Lids | Size:			
Crown | Size:			
Other | Size:			
*Location: | Size:			
Mongolian Spot			
Sacrum			
Back			
Shoulders			
Café-Au-Lait (count only if ≥ 1.5 cm or ≥ 6 CAF spots)			
Nevus Sebaceous			
Hirsuitism			
Dipigmentary Skin Changes			
Other			
Joints			
Contracture			
Laxity			
Dislocation			
Other			
Neurologic			
Hypotonia			
Hypertonia			
Irritability			
Other			

Age:_____

	Measurements:	Percentile	Minor Malf?
OFC			
Palpebral Fissure			
Left			
Right			
Philtrum			
Inner Canthal Distance			

Total Number of Minor Malformations: _____

List Minor Malformations (indicate NC by those not counted):

Major Malformations:

Additional Comments:

Physician Name:_____

Physician Signature:_____