Sponsor: Sanofi **Drug substance(s):** SARILUMAB	**Study Identifiers:** NCT03378219 U1111-1200-1947 **Study code:** OBS15155

Title of the study:

Kevzara® (Sarilumab) Pregnancy Exposure Registry: An OTIS Pregnancy Surveillance Study

Study Center(s):

This study was conducted in the USA and Canada.

Study period:

Date of study start date: 18-May-2018

Date of last study participant completed: 06-Dec-2024

Study Status: Terminated (terminated with approval of the involved health authorities because of very poor enrolment in the exposed patient groups)

Objectives:

Primary Objective:

o To evaluate the relative risk of major structural birth defects (as defined by the Metropolitan Atlanta Congenital Defects Program), specifically a pattern of anomalies, up to one year of age in sarilumab-exposed pregnancies compared to the primary comparison group of disease-matched unexposed pregnancies.

Secondary Objectives:

o To evaluate the risk of sarilumab-exposure relative to the secondary comparison group of healthy pregnant women, and the effect on other adverse pregnancy and infant outcomes:

Pregnancy Outcomes:

- spontaneous abortion,
- stillbirth,
- premature delivery.

Infant Outcomes:

- specific pattern of ≥ 3 minor structural birth defects,
- small for gestational age,
- postnatal growth deficiency,
- serious or opportunistic infections in the first year of life,
- hospitalizations in the first year of life excluding those that are linked to premature delivery or birth defects included as endpoints,
- malignancies identified in the first year of life.

Methodology:

This is a prospective, observational, exposure cohort study of pregnancy outcomes in women with a Kevzara approved indication who are exposed to sarilumab during pregnancy compared with pregnancy outcomes in women with a Kevzara approved indication who have not used sarilumab during pregnancy (Disease Comparison), and pregnancy outcomes in women without a chronic disease thought to impact pregnancy outcome and who have not been exposed to sarilumab or any known human teratogen during pregnancy (Non-Disease Comparison). The Registry cohort study will be conducted by OTIS, which is a network of university and health department-based telephone information centers serving pregnant women and healthcare providers throughout North America.

The study population includes pregnant women with sarilumab exposure for an approved indication anytime between the first day of the last menstrual period up to and including the end of pregnancy, and two comparison groups without sarilumab exposure during pregnancy who reside in the U.S. or Canada. The internal comparison groups are recruited using similar referral sources and are followed in an identical manner to collect exposure, outcome and potential confounder information.

Pregnant women who meet the study exposure and enrolment criteria are recruited for participation in the exposure cohort study. Pregnant women who do not meet the study exposure or enrolment criteria but who are exposed to sarilumab during pregnancy or within 10 weeks prior to the first day of the last menstrual period (LMP), are also asked to enrol as part of the study "Exposure-Series" group so that these data can be used to further illuminate any findings in the cohort study during the course of the project, and when the final analyses are performed.

Number of study participants:

Planned: The overall recruitment goals for the cohort study were set at 100 subjects in each of the 3 cohort groups.

Enrolled: 114 participants were enrolled: 1 participant was enrolled in the Sarilumab-Exposed Cohort and 2 participants were enrolled in the Sarilumab-Exposed Case-Series. A total of 43 participants were enrolled into the Disease Comparison group and 68 participants in the Non-Disease Comparison group

Study participant selection:

Inclusion Criteria

Cohort I: Sarilumab-Exposed Cohort:

- Currently pregnant
- Exposed to Kevzara (sarilumab) for the treatment of an approved Kevzara (sarilumab) indication, for any number of days, any dose, at any time from the first day of the last menstrual period (LMP) up to and including the end of pregnancy
- Agree to conditions and requirements of the study including interview schedule, release of medical records, and the physical examination of live born infants

Cohort II: Disease Comparison Cohort:

- Currently pregnant
- Diagnosed with a Kevzara (sarilumab) approved indication
- Approximately frequency matched to the exposed group by disease indication, validated by medical records, who have not been exposed to Kevzara (sarilumab) at any time in the current pregnancy, and have taken another biologic DMARD medication for their disease within 2 years before the current pregnancy and have an indication for such treatment at enrollment
- Agree to conditions and requirements of the study including interview schedule, release of medical records, and the physical examination of live born infants

Cohort III: Non-Disease Comparison Cohort:

- Currently pregnant
- Not diagnosed with a Kevzara (sarilumab) indication and unexposed to Kevzara (sarilumab) during the course of the current pregnancy
- Agree to conditions and the requirements of the study including interview schedule, release of medical records, and the physical examination of live born infants

Exclusion Criteria

Cohort I: Sarilumab-Exposed Cohort:

- First contact the Registry after prenatal diagnosis of any major structural defect or after pregnancy outcome is known (retrospective data)
- Enrolled in this cohort study with a previous pregnancy
- Exposed to Kevzara (sarilumab) for a condition other than a currently approved indication
- Exposed to another biologic during pregnancy or within 10 weeks prior to the first day of LMP
- Exposure to methotrexate, cyclophosphamide, chlorambucil, or mycophenolate mofetil in pregnancy (ie, any time after LMP), or leflunomide within two years prior to pregnancy unless a blood level below 0 .02 mcg /mL has been documented prior to LMP before the pregnancy

Cohort II: Disease Comparison Cohort:

- First contact the Registry after prenatal diagnosis of any major structural defect or after pregnancy outcome is known (retrospective data)
- Enrolled in this cohort study with a previous pregnancy
- Exposed to Kevzara (sarilumab) during pregnancy or within 10 weeks prior to the first days of LMP
- Exposed to methotrexate, cyclophosphamide, chlorambucil, or mycophenolate mofetil in pregnancy (ie, at anytime after the LMP), or leflunomide within two years prior to pregnancy unless a blood level for leflunomide below 0 .02 mcg /mL has been documented prior to LMP before the pregnancy

Cohort III: Non-Disease Comparison Cohort:

- First contact with the Registry after prenatal diagnosis of any major structural defect or after pregnancy outcome is known (retrospective data)
- Enrolled in this cohort study with a previous pregnancy
- Diagnosed with a serious chronic disease that is thought to adversely impact pregnancy
- Exposed to a known human teratogen during pregnancy and confirmed by the OTIS Research Center

Study products: Sarilumab (KEVZARA®)

Duration of study: Pregnant women who enroll in the study will participate for the duration of that pregnancy. Those who deliver at least one live born infant will participate for 1 year after delivery of that infant.
Criteria for evaluation: Primary Endpoint • Major Structural Birth Defects Secondary Endpoints • Pregnancy Outcomes: Spontaneous abortion Stillbirth Preterm delivery • Infant Outcomes: Specific pattern of >3 or more minor structural birth defects Small for gestational age Postnatal growth deficiency Serious or Opportunistic infections in the first year of life Hospitalizations in the first year of life, excluding those that are linked to premature delivery or birth defects included as endpoints Malignancies identified in the first year of life
Statistical methods: All data, where applicable, will be summarized using descriptive statistics. Categorical variables will be summarized by number and percentage in each category. Missing data will be displayed as a separate category where appropriate. The denominator for all percentages will reflect the number of participants within the cohort. Demographic and baseline characteristics will be summarized descriptively for each cohort. Potential confounders will be selected based on scientific knowledge including literature and medical judgment on possible causal pathways. Standardized mean differences (SMDs) will be calculated and used to check the balance of the covariates between the cohorts. For each of the primary endpoint and secondary endpoints, the primary comparison is between the Kevzara (sarilumab) exposed group and the group with the Kevzara (sarilumab) approved indication (s) not exposed to Kevzara (sarilumab) (Cohort 1 versus Cohort 2). The secondary comparison is between the Kevzara (sarilumab) exposed group and the group of non- disease-matched women (Cohort 1 versus Cohort 3).

For each endpoint and each comparison (primary and secondary), the following analysis will be conducted:

• Crude relative risk:

The relative risk of the analyzed endpoint (eg, major structural birth defect) between cohorts and its 95 % confidence interval will be calculated based on the contingency table of endpoint by cohort, using an asymptotic approach or an exact method when the expected frequency of any of the cells of the contingency table is less than five. If the SMDs suggest that all the covariates are similar, the statistical inference of the comparison on the endpoint between cohorts will be based on the crude relative risk (ie, without adjustment of covariates).

• Relative risk with adjustment of covariates:

If the SMDs suggest that some confounders are not balanced, the propensity scores will be calculated and used in regression adjustment to estimate the relative risk and its 95 % confidence interval. In this case, the results will be the base of the statistical inference of the comparison on the endpoint between cohorts. The propensity score is the probability of being in a particular cohort in the comparison, conditional on measured covariates, and will be calculated using a logistic regression.

Summary:

SUBJECTS ENROLLED IN THE COHORT STUDY WITH PREGNANCY OUTCOME

All subjects enrolled in the cohort study with pregnancy outcome reported are shown by exposure in Table 8.1.

Table 8.1. Enrolled Subjects with Pregnancy Outcome

	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 34) n(%)	Non-Disease-Unexposed (N = 49) n(%)	Total Enrolled (N = 84) n(%)
Number of Pregnant Women with Outcome	1 (100.0)	24 (70.6)	24 (49.0)	49 (58.3)

N: Number of enrolled subjects
% = (n/N) * 100

DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR ENROLLED SUBJECTS WITH PREGNANCY OUTCOME

Demographic and baseline characteristics for all pregnant women with a known pregnancy outcome reported are shown by study cohort in Tables 9.1 to 9.26.

Table 9.1. Maternal Age (Years) at Due Date - Continuous

Age (Years)	Sarilumab-Exposed (N=1)	Disease-Matched Comparison (N=24)	Non-Disease-Unexposed (N=24)
Mean	30.7	33.2	32.0
Standard Deviation	----	3.6	5.4
Minimum	30.7	26.6	20.1
1st quartile	30.7	30.7	29.3
Median	30.7	33.2	31.9
3rd quartile	30.7	35.6	34.5
Maximum	30.7	40.6	46.6

N: Number of subjects with pregnancy outcome

Table 9.2. Maternal Age at Due Date - Categorical

Age Category	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
<25 years	0	0	2 (8.3)
25-29 years	0	5 (20.8)	6 (25.0)
30-34 years	1 (100.0)	10 (41.7)	8 (33.3)
>34 years	0	9 (37.5)	8 (33.3)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.3a. Maternal Ethnicity

Ethnicity Category	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Non-Hispanic	1 (100.0)	23 (95.8)	20 (83.3)
Hispanic	0	1 (4.2)	4 (16.7)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.3b. Maternal Race

Race Category	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
White	0	23 (95.8)	17 (70.8)
Black	0	1 (4.2)	1 (4.2)
Asian/Pacific Islander	1 (100.0)	0	2 (8.3)
Native American	0	0	2 (8.3)
Other	0	0	2 (8.3)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.4a. Paternal Ethnicity

Ethnicity Category	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Non-Hispanic	1 (100.0)	23 (95.8)	17 (70.8)
Hispanic	0	1 (4.2)	7 (29.2)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.4b. Paternal Race

Race Category	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
White	1 (100.0)	21 (87.5)	19 (79.2)
Black	0	1 (4.2)	2 (8.3)
Asian/Pacific Islander	0	0	0
Native American	0	1 (4.2)	0
Other	0	1 (4.2)	3 (12.5)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.5. Maternal Educational Category

Years of Completed Education	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
<12 years	0	0	1 (4.2)
12-15 years	0	0	5 (20.8)
>15 years	1 (100.0)	24 (100.0)	18 (75.0)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.6. Hollingshead Socioeconomic Category[a]

Hollingshead Category	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
1	1 (100.0)	16 (66.7)	12 (50.0)
2	0	5 (20.8)	8 (33.3)
3	0	3 (12.5)	2 (8.3)
4	0	0	2 (8.3)
5	0	0	0

[a]Based on four-factor Hollingshead categories incorporating maternal and paternal education and occupation; highest socioeconomic status category = 1; lowest socioeconomic status category = 5.
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.7. Maternal Pre-Pregnancy Body Mass Index (BMI)[a]

BMI Category	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
<18.5 (underweight)	0	1 (4.2)	2 (8.3)
18.5-24.9 (normal weight)	1 (100.0)	10 (41.7)	12 (50.0)
25-29.9 (overweight)	0	7 (29.2)	4 (16.7)
>=30 (obese)	0	6 (25.0)	6 (25.0)

[a]BMI = kilograms body weight/(height in meters)^2
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.8. Gravidity at Time of Enrollment

Number of Times Ever Pregnant[a]	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
1	0	6 (25.0)	6 (25.0)
2-3	1 (100.0)	14 (58.3)	11 (45.8)
4-5	0	4 (16.7)	6 (25.0)
>=6	0	0	1 (4.2)

[a]Includes current pregnancy
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.9. Parity at Time of Enrollment

Number of Previous Live Birth or Stillbirth Deliveries	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
0	0	8 (33.3)	11 (45.8)
1-2	1 (100.0)	16 (66.7)	11 (45.8)
3-4	0	0	2 (8.3)
>=5	0	0	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.10. Previous Spontaneous Abortions at Time of Enrollment[a]

Number of Previous Pregnancies Ending in Spontaneous Abortion	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
0	1 (100.0)	18 (75.0)	14 (58.3)
1	0	2 (8.3)	7 (29.2)
2	0	1 (4.2)	3 (12.5)
>=3	0	3 (12.5)	0

[a]Includes molar pregnancies, blighted ovum, and ectopic pregnancies
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.11. Previous Elective Terminations at Time of Enrollment

Number of Previous Pregnancies Ending in Elective Termination	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
0	1 (100.0)	23 (95.8)	20 (83.3)
1	0	1 (4.2)	2 (8.3)
2	0	0	1 (4.2)
>=3	0	0	1 (4.2)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.12. Gestational Age (Weeks) of Pregnancy at Time of Enrollment - Continuous

Weeks' Gestation	Sarilumab-Exposed (N=1)	Disease-Matched Comparison (N=24)	Non-Disease-Unexposed (N=24)
Mean	36.0	27.6	17.0
Standard Deviation	----	8.9	6.6
Minimum	36.0	6.0	7.1
1st quartile	36.0	22.1	12.7
Median	36.0	30.0	16.3
3rd quartile	36.0	34.3	22.4
Maximum	36.0	39.1	29.7

N: Number of subjects with pregnancy outcome

Table 9.13. Gestational Age of Pregnancy at Time of Enrollment - Categorical

Weeks' Gestation Category	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
<13 weeks	0	1 (4.2)	8 (33.3)
13-19.9 weeks	0	3 (12.5)	9 (37.5)
>=20 weeks	1 (100.0)	20 (83.3)	7 (29.2)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.14. Geographic Area of Residence

Country	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
U.S.	1 (100.0)	20 (83.3)	24 (100.0)
Canada	0	4 (16.7)	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.15. Disease Severity Scores by Exposure Group in Pregnancy

Severity Measure in Pregnancy	Sarilumab-Exposed (N=1)	Disease-Matched Comparison (N=24)
Intake - RA 1[a]	N'= 1	N'= 24
Mean	0.4	0.3
Standard deviation	----	0.4
Minimum	0.4	0.0
1st quartile	0.4	0.0
Median	0.4	0.1
3rd quartile	0.4	0.5
Maximum	0.4	1.5
Intake - RA 2[b]	N'= 1	N'= 24
Mean	20.0	22.7
Standard deviation	----	25.0
Minimum	20.0	0.0
1st quartile	20.0	4.8
Median	20.0	12.5
3rd quartile	20.0	30.0
Maximum	20.0	85.0
Intake - RA 3[c]	N'= 1	N'= 24
Mean	15.0	22.1
Standard deviation	----	23.9
Minimum	15.0	0.0
1st quartile	15.0	2.8
Median	15.0	15.0
3rd quartile	15.0	32.5
Maximum	15.0	80.0
3rd Trimester (32 week) - RA 1[a]	N'= 0	N'= 11
Mean	----	0.2
Standard deviation	----	0.2
Minimum	----	0.0
1st quartile	----	0.0
Median	----	0.1
3rd quartile	----	0.4
Maximum	----	0.6
3rd Trimester (32 week) - RA 2[b]	N'= 0	N'= 11
Mean	----	13.3
Standard deviation	----	16.4
Minimum	----	0.0
1st quartile	----	3.5
Median	----	7.0
3rd quartile	----	15.0
Maximum	----	55.0

Severity Measure in Pregnancy	Sarilumab-Exposed (N=1)	Disease-Matched Comparison (N=24)
3rd Trimester (32 week) - RA 3[c]	N'= 0	N'= 11
Mean	----	9.5
Standard deviation	----	11.2
Minimum	----	0.0
1st quartile	----	0.5
Median	----	5.0
3rd quartile	----	15.0
Maximum	----	35.0

[a]Rheumatoid Arthritis (RA) 1: maternal report of interference with usual abilities; possible score 0-60 with higher score indicating more interference
[b]Rheumatoid Arthritis (RA) 2: maternal report of experience of disease-related pain; possible score 0-100 with higher score indicating more pain
[c]Rheumatoid Arthritis (RA) 3: maternal report of how overall illness affects her; possible score 0-100 with higher score indicating more effect
N: Number of women with pregnancy outcome
N': Number of subjects enrolled with completed questionnaire on each severity measure

Table 9.16. Prenatal, Multivitamin or Folic Acid Supplement Use and Timing in Pregnancy

Timing of Vitamin Use	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Began prior to conception	1 (100.0)	20 (83.3)	11 (45.8)
Post-conception only	0	4 (16.7)	13 (54.2)
Have not taken at all	0	0	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.17. Alcohol Use in Pregnancy

Any Alcohol in Pregnancy (post-conception)	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Yes	0	8 (33.3)	6 (25.0)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.18. Tobacco Use in Pregnancy

Any Tobacco Smoked in Pregnancy (post-conception)	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Yes	0	0	1 (4.2)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.19. Systemic Steroid Use in Pregnancy

Any Systemic Steroid in Pregnancy (post-conception)	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Yes	1 (100.0)	8 (33.3)	0

Table 9.20. Methotrexate Use in Pregnancy

Any Methotrexate in Pregnancy (post-conception)	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Yes	0	0	0

Table 9.21. Exposure to Major Known or Suspected Human Teratogens

Major Known or Suspected Human Teratogens in Pregnancy (post-conception)	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Yes	0	1 (4.2)	0

[a]One woman in the Disease Matched Comparison group was exposed to Lithium during her pregnancy.
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.22. Dose Treatment Used between LMP and Pregnancy Outcome (1st Treatment Dose if Multiple Doses Occurred)

Dose and Frequency of Sarilumab	Sarilumab-Exposed (N = 1) n(%)
200 mg every two weeks	0
150 mg every two weeks	1 (100.0)
Other	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.23. Weeks' Post-Conception of Last Dose of Sarilumab in Pregnancy

Dose and Frequency of Sarilumab	Sarilumab-Exposed (N=1)
Mean	36.4
Standard Deviation	----
Minimum	36.4
1st quartile	36.4
Median	36.4
3rd quartile	36.4
Maximum	36.4

Table 9.24. Gestational Timing of Sarilumab Use in Pregnancy[a]

Trimester of Medication Use in Pregnancy	Sarilumab-Exposed (N = 1) n(%)
Exposure Prior to LMP	0
LMP to < DOC only[b]	0
1st Trimester only	0
1st and 2nd Trimesters only	0
1st and 3rd Trimesters only	0
1st, 2nd, and 3rd Trimesters only	0
2nd Trimester only	0
2nd and 3rd Trimesters only	0
3rd Trimester only	1 (100.0)

[a]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 subject is exposed in both LMP to DOC and the 1st trimester, she will be in the category of '1st Trimester'

[b]Last dose occurred in [LMP, DOC)

N: Number of subjects with pregnancy outcome

% = (n/N) * 100

Table 9.25. Prenatal Diagnostic Tests Performed Anytime during Pregnancy

	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Ultrasound Level 1	1 (100.0)	24 (100.0)	22 (91.7)
Ultrasound Level 2	1 (100.0)	24 (100.0)	22 (91.7)
Chorionic villus sampling (CVS)	0	0	0
Amniocentesis	0	0	0

N: Number of subjects with pregnancy outcome

% = (n/N) * 100

Table 9.26. Prenatal Diagnostic Tests Performed prior to Enrollment

	Sarilumab-Exposed (N = 1) n(%)	Disease-Matched Comparison (N = 24) n(%)	Non-Disease-Unexposed (N = 24) n(%)
Ultrasound Level 1	1 (100.0)	23 (95.8)	20 (83.3)
Ultrasound Level 2	1 (100.0)	20 (83.3)	5 (20.8)
Chorionic villus sampling (CVS)	0	0	0
Amniocentesis	0	0	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

PREGNANCY OUTCOMES IN WOMEN ENROLLED IN THE COHORT STUDY

Pregnancy and infant outcome information for all subjects reported shown by study cohort in Tables 10.1 to 10.14. N is those with outcome, N' is those in the cohort who are eligible for an outcome being described and n represents the number with that event (numerator).

Table 10 .1. Pregnancy Outcome

	Sarilumab Exposed Cohort	Sarilumab Exposed Case-Series	Diseased-Matched Comparison	Non-Diseased Unexposed	Total
Known Pregnancy Outcome	**1**	**2**	**37**	**48**	**88**
Live born	1	2	37	46	86
SAB[1]	0	0	0	2	2
Stillbirth	0	0	0	0	0
TAB[2]	0	0	0	0	0
LTFU[3] Outcome	**0**	**0**	**0**	**3**	**3**
No Contact	0	0	0	1	1
Withdrew	0	0	0	2	2
Pending Outcome	**0**	**0**	**6**	**17**	**23**
Total:	**1**	**2**	**43**	**68**	**114**

1. Spontaneous abortion (SAB)

2. Termination of pregnancy (TAB)

3. Lost-to Follow-up (LTFU)

No major malformations have been confirmed in the Sarilumab-Exposed Cohort or Sarilumab Case-Series groups. No neonatal deaths have been reported.

Table 2: Cumulative Listing of Events Reported in the Sarilumab-Exposed Pregnancies

Pregnancy ID / Outcome ID	Cohort or Case-Series Group	Description of Event / Outcome
99580 / 8319	Cohort	Sarilumab exposure preconception and third trimester. 200 mg 2x per month ongoing to 4.5 weeks prior to conception. 150 mg 2x per month from 27.9 to 31.9 weeks post-conception. 200 mg 2x per month 33.9 weeks post-conception to delivery. Child born full-term at 38.4 weeks' gestation. with a birth weight of 3370 grams, birth length of 53.34 cm, and a birth head circumference of 33 cm. Pregnancy resulted in normal outcomes for all study endpoints.
110010 / 8729	Case-Series	Sarilumab exposure third trimester. Dose and frequency unknown. Excluded from the Cohort for the reason: 1) Enrolled retrospectively, 2) Does not have study related disease The participant was exposed to sarilumab in the third trimester for treatment of maternal COVID-19 infection. Preterm infant born at 30.4 weeks' gestation after participant was hospitalized and intubated for COVID-19 infection. Birth weight was 1871 grams, birth length was 43.2 cm, birth head circumference was unknown. All other study endpoints were normal.
147283 / 21107	Case-Series	Sarilumab first trimester exposure. 200 mg 2x per month ongoing to 1.5 weeks prior to conception. 150 mg 2x per month from 1.4 weeks prior to conception to 6.1 weeks post-conception. Excluded from the Cohort for the reason: Exposure to disqualifying medications during pregnancy (etanercept and certolizumab pegol) All outcome information obtained by maternal report.

		Child born at 37.0 weeks' gestation, with a birth weight of 3260 grams, birth length of 49.5 cm, and birth head circumference of 36.8 cm. Child was diagnosed at 7 months with global developmental delay. He was found to have global white matter volume loss after MRI, which was concerning for an in-utero hypoperfusion event. Extensive work-up excluded metabolic or genetic cause. Whole exome sequencing was normal. MRI pattern was noted to be similar to hypoxic-ischemic encephalopathy. No further information on diagnosis received. Child was hospitalized on multiple occasions in the first 2 months of life for diagnostic procedures, including MRI, CT and EEG. Pregnancy and Health History: • Maternal age of 42 at EDC • BMI of 39.5 • History of recurrent spontaneous abortion (6) and 1 ectopic pregnancy • One live born infant delivered preterm. Pregnancy diagnosed with preeclampsia and gestational diabetes. • IVF pregnancy (current pregnancy) Pregnancy Complications / Events / Concomitant Interventions: • Per maternal report diagnosed with gestational hypertension and gestational diabetes • Participant was hospitalized at approximately 5 weeks' gestation for gallbladder removal surgery due to cholecystitis. Participant had several x-rays, 2 MRIs and endoscopic retrograde cholangiopancreatography (ECRP) for diagnostic purposes. • COVID-19 infection treated with bebtelovimab • Treatment for RA during pregnancy included certolizumab pegol (first, second, and third trimesters) and etanercept (first and third trimesters) •

Table 10.2. Spontaneous Abortion (SAB) among Women Prospectively Enrolled and Exposed prior to 20 Weeks' Gestation and with Follow Up

	Sarilumab Exposed (N=0)	Disease-Matched Comparison (N=4)	Non-Diseased Unexposed (N=16)
Number of SAB Events[a]	0	0	1
Left Truncation Accounted SAB Rate[b,c,d,e]	----	0.0%	8.1%

[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]One LTFU case was excluded due to having zero days of follow-up: 1 Non-Disease-Matched Comparison.
[d]Gestational age at Delivery (GAD) was missing for 1 SAB case. Multiple imputation was conducted for cases with missing GAD. The number of imputations was 10.
[e]Earliest gestational age at enrollment (weeks): Disease-Matched Comparison 6, Non-Disease-Matched Comparison 7.1.
N: Number of subjects enrolled and exposed prior to 20 weeks' gestation and with follow up.

Table 10.3. Major Birth Defects

	Sarilumab-Exposed n/N(%)	Disease-Matched Comparison n/N(%)	Non-Disease-Unexposed n/N(%)
Number of pregnancies ending with at least one live born infant with a major birth defect	0/1 (0.0)	0/24 (0.0)	0/22 (0.0)
Number of all pregnancies (excluding LTFU) with major birth defects	0/1 (0.0)	0/24 (0.0)	0/23 (0.0)

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

10.3a Major Birth Defects Among Pregnancies with Multiple Births

	Sarilumab-Exposed n/N(%)	Disease-Matched Comparison n/N(%)	Non-Disease-Unexposed n/N(%)
Number of pregnancies ending with at least one live born infant with a major birth defect	----	----	----
Number of all pregnancies (excluding LTFU) with major birth defects	----	----	----

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

Table 10.4. Major Birth Defects among Pregnancies Compared to Population Reference

	Sarilumab-Exposed n/N(%)	MACDP Reference Rate[a] (%)
Birth Prevalence of major birth defects among all pregnancies excluding LTFU	0/1 (0.0)	---
Birth Prevalence of major birth defects among all pregnancies, excluding LTFU and SAB	0/1 (0.0)	3.0

[a]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 pregnancies with defects can be of any gestational age; in any live born infant, a birth defect must be identified by the child's sixth birthday.

Table 10.5. Number of Infants with a Pattern of Minor Malformations among All Infants Receiving Dysmorphological Examination

	Sarilumab-Exposed n/N(%)	Disease-Matched Comparison n/N(%)	Non-Disease-Unexposed n/N(%)
Number of infants who received the Exam/Number of infants eligible for Exam	0/1 (0.0)	0/24 (0.0)	2/22 (9.1)
Number of infants examined with at least 3 or more of any minor malformations[a]	---	---	0/2 (0.0)
Number of infants examined with a pattern of 3 or more minor malformations[b]	---	---	0/2 (0.0)

[a]Includes singletons and multiples who received the dysmorphological exam

[b]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 10.6. Preterm Delivery among Pregnancies 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)

	Sarilumab Exposed (N=1)	Disease-Matched Comparison (N=20)	Non-Diseased Unexposed (N=22)
Number of PTD (n)	0	2	2
Left Truncation Accounted PTD Rate[a,b]	0.0%	10.3%	8.9%

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

[b]One case in the Non-Disease-Matched Comparison Group was excluded due to having zero days of follow-up.

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

Table 10.7. Gestational Age (Weeks) At Delivery among Pregnancies Ending in Live Birth (Multiple Births Excluded)

	Sarilumab-Exposed (N=1)	Disease-Matched Comparison (N=24)	Non-Disease-Unexposed (N=22)
Mean	38.4	39.0	39.0
Standard Deviation	----	1.4	1.3
Minimum	38.4	35.1	36.7
1st quartile	38.4	38.1	38.1
Median	38.4	39.1	39.1
3rd quartile	38.4	40.0	39.8
Maximum	38.4	40.9	41.3

N: Number of pregnancies resulting in a live born infant, multiple births excluded.

10.8 Preeclampsia and Pregnancy Induced Hypertension (PIH) among Pregnancies Ending in Live Birth

	Sarilumab-Exposed (N=1) n/N'(%)	Disease-Matched Comparison (N=24) n/N'(%)	Non-Disease-Unexposed (N=22) n/N'(%)
Preeclampsia	0/1 (0.0)	1/24 (4.2)	0/22 (0.0)
PIH	0/1 (0.0)	2/23 (8.7)	1/22 (4.5)

% = (n/N') * 100. N' at each category: Number of pregnancies ending with at least one live born and for whom the preeclampsia/PIH information is available.

Table 10.9. Birth Size for Full Term Infants (Multiple Births Excluded)

	Sarilumab-Exposed (N=1)	Disease-Matched Comparison (N=22)	Non-Disease-Unexposed (N=20)
Birth Weight - grams	N'= 1	N'= 22	N'= 20
Mean	3370.0	3435.2	3257.2
Standard deviation	--	401.1	368.2
Minimum	3370.0	2470.0	2597.0
1st quartile	3370.0	3222.5	3001.7
Median	3370.0	3495.0	3175.1
3rd quartile	3370.0	3690.1	3444.5
Maximum	3370.0	4054.0	4105.0
Birth Length - cm	N'= 1	N'= 21	N'= 20
Mean	53.3	51.0	51.0
Standard deviation	--	2.7	2.2
Minimum	53.3	45.0	45.7
1st quartile	53.3	50.0	49.5
Median	53.3	52.0	51.0
3rd quartile	53.3	53.0	52.4
Maximum	53.3	54.6	55.9
Birth Occipitofrontal Circumference - cm	N'= 1	N'= 14	N'= 14
Mean	33.0	34.4	34.3
Standard deviation	--	1.5	1.1
Minimum	33.0	31.0	33.0
1st quartile	33.0	34.0	33.0
Median	33.0	34.5	34.5
3rd quartile	33.0	35.0	35.0
Maximum	33.0	37.0	36.0

N: Number of full term singletons

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

Table 10.10. Small for Gestational Age (SGA) at Birth Among Live Born Infants (Multiple Pregnancies Excluded)[a]

	Sarilumab-Exposed (N=1) n/N'(%)	Disease-Matched Comparison (N=24) n/N'(%)	Non-Disease-Unexposed (N=22) n/N'(%)
Weight	0/1 (0.0)	2/24 (8.3)	1/22 (4.5)
Length	0/1 (0.0)	2/22 (9.1)	1/22 (4.5)
Occipitofrontal Circumference (OFC)	1/1 (100.0)	2/14 (14.3)	3/14 (21.4)
SGA weight and/or length, but not OFC	0/1 (0.0)	1/21 (4.8)	1/22 (4.5)
SGA weight and/or length, and OFC	0/1 (0.0)	1/21 (4.8)	0/22 (0.0)

[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 10.11. Postnatal Growth Percentile at One Year - Continuous (Multiple Births Excluded)

	Sarilumab-Exposed (N=1)	Disease-Matched Comparison (N=16)	Non-Disease-Unexposed (N=10)
Weight - percentile	N'= 0	N'= 3	N'= 4
Mean	----	32.7	20.8
Standard deviation	----	35.8	19.2
Minimum	----	11.0	3.0
1st quartile	----	12.0	5.2
Median	----	13.0	19.0
3rd quartile	----	43.5	34.5
Maximum	----	74.0	42.0
Length - percentile	N'= 0	N'= 3	N'= 4
Mean	----	59.0	53.0
Standard deviation	----	15.7	21.2
Minimum	----	42.0	31.0
1st quartile	----	52.0	43.8
Median	----	62.0	49.5
3rd quartile	----	67.5	58.8
Maximum	----	73.0	82.0
Occipitofrontal Circumference - percentile	N'= 0	N'= 3	N'= 4
Mean	----	48.4	41.0
Standard deviation	----	49.0	33.2
Minimum	----	0.1	12.0
1st quartile	----	23.6	21.8
Median	----	47.0	32.0
3rd quartile	----	72.5	51.2
Maximum	----	98.0	88.0

Age adjusted if child is less than 12 months, unadjusted if >=12 months. Measurements are 12 months of age ± 3 months.

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

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

Table 10.12. Postnatal Growth One Year - Percentile <=10th (Multiple Births Excluded)

	Sarilumab-Exposed (N=1) n/N'(%)	Disease-Matched Comparison (N=16) n/N'(%)	Non-Disease-Unexposed (N=10) n/N'(%)
Weight <=10th centile[a]	---	0/3 (0.0)	2/4 (50.0)
Length <=10th centile[a]	---	0/3 (0.0)	0/4 (0.0)
Occipitofrontal Circumference <=10th centile[a]	---	1/3 (33.3)	0/4 (0.0)

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

Table 10.13. Postnatal Events - Serious and Opportunistic Infections in Infants up to One Year of Age (Including Infants from Multiple Births)

	Sarilumab-Exposed (N=1) n/N'(%)	Disease-Matched Comparison (N=24) n/N'(%)	Non-Disease-Unexposed (N=22) n/N'(%)
Yes	0/1 (0.0)	0/24 (0.0)	1/22 (4.5)

N at column heading: Number of live born singletons.
% = (n/N') * 100; N': Number of live born infants with the event information available.

Table 10.14. Postnatal Events - Malignancies in Infants up to One Year of Age (Including Infants from Multiple Births)

	Sarilumab-Exposed (N=1) n/N'(%)	Disease-Matched Comparison (N=24) n/N'(%)	Non-Disease-Unexposed (N=22) n/N'(%)
Yes	0/1 (0.0)	0/24 (0.0)	0/22 (0.0)

N at column heading: Number of live born singletons.
% = (n/N') * 100; N': Number of live born infants with the event information available.

No major malformations were detected and no Neonatal or Infant Death occurred in all cohorts.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR ENROLLED SARILUMAB - EXPOSED REGISTRY CASE SERIES WITH PREGNANCY OUTCOME

Demographic and baseline characteristics for enrolled Sarilumab-exposed registry case series are shown in Tables 12.1 to 12.24. In Section 12 tables, % = (n/N) * 100; N is the number of subjects enrolled in the cohort with available outcome (denominator), and "n" represents the number with that event as described in the row heading (numerator).

Table 12.1 Reasons for Exclusion from the Sarilumab Exposed Cohort

Reasons for exclusion from the cohort[a]:	Sarilumab Exposed Case-Series (N = 1) n/N'(%)
Preconception exposure (last dose between LMP and <DOC)	0/1 (0.0)
Prenatal diagnosis of a major malformation prior to enrollment	0/1 (0.0)
Retrospective	1/1 (100.0)
Exclusionary medication	0/1 (0.0)
Previous enrollment in the Cohort	0/1 (0.0)
Not diagnosed with RA	1/1 (100.0)

[a]Participants may be included in more than one category
N: Number of subjects enrolled in the registry group.
N': Number of subjects enrolled in the registry group and with information available.

Table 12.2. Maternal Age (Years) at Due Date - Continuous

Age (Years)	Sarilumab-Exposed Case-Series (N=1)
Mean	31.7
Standard Deviation	--
Minimum	31.7
1st quartile	31.7
Median	31.7
3rd quartile	31.7
Maximum	31.7

N: Number of subjects with pregnancy outcome

Table 12.3. Maternal Age at Due Date - Categorical

Age Category	Sarilumab-Exposed Case-Series (N = 1) n(%)
<25 years	0
25-29 years	0
30-34 years	1 (100.0)
>34 years	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.4a. Maternal Ethnicity

Ethnicity Category	Sarilumab-Exposed Case-Series (N = 1) n(%)
Non-Hispanic	0
Hispanic	1 (100.0)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.4b. Maternal Race

Race Category	Sarilumab-Exposed Case-Series (N = 1) n(%)
White	1 (100.0)
Black	0
Asian/Pacific Islander	0
Native American	0
Other	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.5a. Paternal Ethnicity

Ethnicity Category	Sarilumab-Exposed Case-Series (N = 1) n(%)
Non-Hispanic	0
Hispanic	1 (100.0)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.5b. Paternal Race

Race Category	Sarilumab-Exposed Case-Series (N = 1) n(%)
White	0
Black	0
Asian/Pacific Islander	0
Native American	0
Other	1 (100.0)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.6. Maternal Educational Category

Years of Completed Education	Sarilumab-Exposed Case-Series (N = 1) n(%)
<12 years	0
12-15 years	1 (100.0)
>15 years	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.7. Hollingshead Socioeconomic Category[a]

Hollingshead Category	Sarilumab-Exposed Case-Series (N = 1) n(%)
1	1 (100.0)
2	0
3	0
4	0
5	0

[a]Based on four-factor Hollingshead categories incorporating maternal and paternal education and occupation; highest socioeconomic status category = 1; lowest socioeconomic status category = 5.
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.8. Maternal Pre-Pregnancy Body Mass Index (BMI)[a]

BMI Category	Sarilumab-Exposed Case-Series (N = 1) n(%)
<18.5 (underweight)	0
18.5-24.9 (normal weight)	0
25-29.9 (overweight)	0
>=30 (obese)	1 (100.0)

[a]BMI = kilograms body weight/(height in meters)^2
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.9. Gravidity at Time of Enrollment

Number of Times Ever Pregnant[a]	Sarilumab-Exposed Case-Series (N = 1) n(%)
1	0
2-3	1 (100.0)
4-5	0
>=6	0

[a]Includes current pregnancy
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.10. Parity at Time of Enrollment

Number of Previous Live Birth or Stillbirth Deliveries	Sarilumab-Exposed Case-Series (N = 1) n(%)
0	0
1-2	1 (100.0)
3-4	0
>=5	0

Table 12.11. Previous Spontaneous Abortions at Time of Enrollment[a]

Number of Previous Pregnancies Ending in Spontaneous Abortion	Sarilumab-Exposed Case-Series (N = 1) n(%)
0	1 (100.0)
1	0
2	0
>=3	0

[a]Includes molar pregnancies, blighted ovum, and ectopic pregnancies
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.12. Previous Elective Terminations at Time of Enrollment

Number of Previous Pregnancies Ending in Elective Termination	Sarilumab-Exposed Case-Series (N = 1) n(%)
0	1 (100.0)
1	0
2	0
>=3	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.13. Geographic Area of Residence

Country	Sarilumab-Exposed Case-Series (N = 1) n(%)
U.S.	1 (100.0)
Canada	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.14. Prenatal, Multivitamin or Folic Acid Supplement Use and Timing in Pregnancy

Timing of Vitamin Use	Sarilumab-Exposed Case-Series (N = 1) n(%)
Began prior to conception	1 (100.0)
Post-conception only	0
Have not taken at all	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.15. Alcohol Use in Pregnancy

Any Alcohol in Pregnancy (post-conception)	Sarilumab-Exposed Case-Series (N = 1) n(%)
Yes	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.16. Tobacco Use in Pregnancy

Any Tobacco Smoked in Pregnancy (post-conception)	Sarilumab-Exposed Case-Series (N = 1) n(%)
Yes	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.17. Systemic Steroid Use in Pregnancy

Any Systemic Steroid in Pregnancy (post-conception)	Sarilumab-Exposed Case-Series (N = 1) n(%)
Yes	0

Table 12.18. Methotrexate Use in Pregnancy

Any Methotrexate in Pregnancy (post-conception)	Sarilumab-Exposed Case-Series (N = 1) n(%)
Yes	0

Table 12.19 Exposure to Major Known or Suspected Human Teratogens

Major Known or Suspected Human Teratogens in Pregnancy (post-conception)	Sarilumab-Exposed Case-Series (N = 1) n(%)
Yes	1 (100.0)

[a]One woman with fever ≥102.0 degrees Fahrenheit in third trimester (due to COVID-19 infection). Fever for 3.5 weeks, but unsure the number of hours or days above 102.0 degrees
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.20. Dose Treatment Used between LMP and Pregnancy Outcome (1st Treatment Dose if Multiple Doses Occurred)

Dose and Frequency of Sarilumab	Sarilumab-Exposed Case-Series (N = 1) n(%)
Data Available	0
200 mg every two weeks	----
150 mg every two weeks	----
Other	----

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.21. Weeks' Post-Conception of Last Dose of Sarilumab in Pregnancy

Dose and Frequency of Sarilumab	Sarilumab-Exposed Case-Series (N=1)
Mean	30.4
Standard Deviation	----
Minimum	30.4
1st quartile	30.4
Median	30.4
3rd quartile	30.4
Maximum	30.4

Table 12.22. Gestational Timing of Sarilumab Use in Pregnancy[a]

Trimester of Medication Use in Pregnancy	Sarilumab-Exposed Case-Series (N = 1) n(%)
Exposure Prior to LMP	0
LMP to < DOC only[b]	0
1st Trimester only	0
1st and 2nd Trimesters only	0
1st and 3rd Trimesters only	0
1st, 2nd, and 3rd Trimesters only	0
2nd Trimester only	0
2nd and 3rd Trimesters only	0
3rd Trimester only	1 (100.0)

[a]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 subject is exposed in both LMP to DOC and the 1st trimester, she will be in the category of '1st Trimester'
[b]Last dose occurred in [LMP, DOC)
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.23. Prenatal Diagnostic Tests Performed Anytime During Pregnancy

	Sarilumab-Exposed Case-Series (N = 1) n(%)
Ultrasound Level 1	1 (100.0)
Ultrasound Level 2	0
Chorionic villus sampling (CVS)	0
Amniocentesis	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 12.24. Prenatal Diagnostic Tests Performed Prior to Enrollment

	Sarilumab-Exposed Case-Series (N = 1) n(%)
Ultrasound Level 1	1 (100.0)
Ultrasound Level 2	0
Chorionic villus sampling (CVS)	0
Amniocentesis	0

N: Number of subjects with pregnancy outcome
% = (n/N) * 100

PREGNANCY OUTCOMES FOR WOMEN ENROLLED IN THE SARILUMAB-EXPOSED REGISTRY CASE-SERIES

Pregnancy outcome information for all subjects enrolled in the registry case-series are shown in the Registry in Tables 13.1 to 13.14. N is those with outcome, N' is those in the overall sample that are eligible for an outcome being described, and n represents the number with that event (numerator).

Table 13.1. Pregnancy Outcome

	Sarilumab-Exposed Case-Series (N=1) n/N'(%)
Live birth	1/1 (100.0)
Twin	0/1 (0.0)
Twin with like sex	----
Sex (male)	----
Twin with non like sex	----
Twin with only one surviving	----
Sex (male)	----
Singleton	1/1 (100.0)
Sex (male)	1/1 (100.0)
Cesarean	1/1 (100.0)
Spontaneous Abortion[a]	0/1
Spontaneous Abortion-Twins	----
Stillbirth	0/1 (0.0)
Termination	0/1 (0.0)
Social	----
Medical	----
Lost to Follow Up	0/1 (0.0)
No Contact	----
Withdrew	----

N: Number of subjects with pregnancy outcome
n/N' (%) is either out of total N or % of the N' subcategories under the live birth, termination or lost to follow-up rows.
[a]Left Truncation Accounted SAB Rate in Table 13.2.

Table 13.2 Spontaneous Abortion (SAB) among Women Prospectively Enrolled and Exposed Prior to 20 Weeks' Gestation and with Follow Up

	Sarilumab Exposed Case-Series (N=0)
Number of SAB Events[a]	0
Left Truncation Accounted SAB Rate[b,c]	----

[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]0 out of 1 retrospective cases ended in SAB.
N: Number of subjects enrolled and exposed prior to 20 weeks' gestation and with follow up.

Table 13.3a. Major Birth Defects

	Sarilumab-Exposed Case-Series n/N(%)
Number of pregnancies ending with at least one live born infant with a major birth defect	0/1 (0.0)
Number of all pregnancies (excluding LTFU) with major birth defects	0/1 (0.0)

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

13.3b Major Birth Defects Among Pregnancies with Multiple Births

	Sarilumab-Exposed Case-Series n/N(%)
Number of pregnancies ending with at least one live born infant with a major birth defect	---
Number of all pregnancies (excluding LTFU) with major birth defects	---

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

Table 13.4. Major Birth Defects Among Pregnancies Compared to Population Reference

	Sarilumab-Exposed Case-Series n/N(%)	MACDP Reference Rate[a](%)
Birth Prevalence of major birth defects among all pregnancies excluding LTFU	0/1 (0.0)	---
Birth Prevalence of major birth defects among all pregnancies, excluding LTFU and SAB	0/1 (0.0)	3.0

[a]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 pregnancies with defects can be of any gestational age; in any live born infant, a birth defect must be identified by the child's sixth birthday.

Table 13.5. Number of Infants with a Pattern of Minor Malformations among All Infants Receiving Dysmorphological Examination

	Sarilumab-Exposed Case-Series n/N(%)
Number of infants who received the Exam/Number of infants eligible for Exam	---
Number of infants examined with at least 3 or more of any minor malformations[a]	---
Number of infants examined with a pattern of 3 or more minor malformations[b]	---

[a]Includes singletons and multiples who received the dysmorphological exam

[b]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 13.6. Preterm Delivery 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)

	Sarilumab Exposed Case-Series (N=0)
Number of PTD (n)	0
Left Truncation Accounted PTD Rate[a,b]	--

[a]Computed using Fleming-Harrington estimate at 37 weeks gestation, accounting for left truncation due to varying time in gestation at enrollment.

[b]0 cases were excluded due to having zero days of follow-up.

1 out of 1 retrospective cases ended in PTD.

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

Table 13.7. Gestational Age (Weeks) At Delivery among Pregnancies Ending in Live Birth (Multiple Births Excluded)

	Sarilumab-Exposed Case-Series (N=1)
Mean	30.4
Standard Deviation	----
Minimum	30.4
1st quartile	30.4
Median	30.4
3rd quartile	30.4
Maximum	30.4

N: Number of pregnancies resulting in a live born infant, multiple births excluded.

13.8 Preeclampsia and Pregnancy Induced Hypertension (PIH) among Pregnancies Ending in Live Birth

	Sarilumab-Exposed Case-Series (N=1) n/N'(%)
Preeclampsia	0/1 (0.0)
PIH	0/1 (0.0)

% = (n/N') * 100. N' at each category: Number of pregnancies ending with at least one live born and for whom the preeclampsia/PIH information is available.

Table 13.9. Birth Size for Full Term Infants (Multiple Births Excluded)

	Sarilumab-Exposed Case-Series (N=0)
Birth Weight - grams	N'= 0
Mean	---
Standard deviation	---
Minimum	---
1st quartile	---
Median	---
3rd quartile	---
Maximum	---
Birth Length - cm	N'= 0
Mean	---
Standard deviation	---
Minimum	---
1st quartile	---
Median	---
3rd quartile	---
Maximum	---
Birth Occipitofrontal Circumference - cm	N'= 0
Mean	---
Standard deviation	---
Minimum	---
1st quartile	---
Median	---
3rd quartile	---
Maximum	---

N: Number of single pregnancies resulting in at least one full term infant

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

Table 13.10. Small for Gestational Age (SGA) at Birth Among Live Born Infants (Multiple Pregnancies Excluded)[a]

	Sarilumab-Exposed Case-Series (N=1) n/N'(%)
Weight	0/1 (0.0)
Length	0/1 (0.0)
Occipitofrontal Circumference (OFC)	---
SGA weight and/or length, but not OFC	0/1 (0.0)
SGA weight and/or length, and OFC	0/1 (0.0)

[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 13.11. Postnatal Growth Percentile at One Year - Continuous (Multiple Births Excluded)

	Sarilumab-Exposed Case-Series (N=1)
Weight - percentile	N'= 0
Mean	—
Standard deviation	—
Minimum	—
1st quartile	—
Median	—
3rd quartile	—
Maximum	—
Length - percentile	N'= 0
Mean	—
Standard deviation	—
Minimum	—
1st quartile	—
Median	—
3rd quartile	—
Maximum	—
Occipitofrontal Circumference - percentile	N'= 0
Mean	—
Standard deviation	—
Minimum	—
1st quartile	—
Median	—
3rd quartile	—
Maximum	—

Age adjusted if child is less than 12 months, unadjusted if >=12 months. Measurements are 12 months of age ± 3 months.

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

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

Table 13.12. Postnatal Growth One Year - Percentile <=10th (Multiple Births Excluded)

	Sarilumab-Exposed Case-Series (N=1) n/N'(%)
Weight <=10th centile[a]	----
Length <=10th centile[a]	----
Occipitofrontal Circumference <=10th centile[a]	----

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

Table 13.13. Postnatal Events - Serious and Opportunistic Infections in Infants up to One Year of Age (Including Infants from Multiple Births)

	Sarilumab-Exposed Case-Series (N=1) n/N'(%)
Yes	0/1 (0.0)

N at column heading: Number of live born singletons.
% = (n/N') * 100; N': Number of live born infants with the event information available.

Table 13.14. Postnatal Events - Malignancies in Infants up to One Year of Age (Including Infants from Multiple Births)

	Sarilumab-Exposed Case-Series (N=1) n/N'(%)
Yes	0/1 (0.0)

N at column heading: Number of live born singletons.
% = (n/N') * 100; N': Number of live born infants with the event information available.

No major malformations were detected, no serious or opportunistic infections, no malignancies, and no neonatal or infant death occurred in any cohorts.

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