The Benralizumab Pregnancy Exposure Study: A VAMPSS Post-Marketing Surveillance Study

2019 Final Annual Interim Report

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Contents

Appendices

Abbreviation or special term	Explanation
AAAAI	American Academy of Allergy, Asthma and Immunology
AZ	AstraZeneca
BMI	Body Mass Index
CDC	Centers for Disease Control and Prevention
CVS	Chorionic Villus Sampling
DOC	Date of Conception
GA	Gestational Age
GINA	Global Initiative for Asthma
LMP	Last Menstrual Period
LTFU	Lost-to Follow-up
MACDP	Metropolitan Atlanta Congenital Defects Program
OFC	Head Circumference
OTIS	Organization of Teratology Information Services
PIH	Pregnancy Induced Hypertension
PTD	Preterm Delivery
SAB	Spontaneous Abortion
SGA	Small for Gestational Age
UCSD	University of California, San Diego
US	United States
VAMPSS	Vaccines and Medications in Pregnancy Surveillance System

1 PURPOSE AND RATIONALE FOR THE REGISTRY

The purpose of the Benralizumab Pregnancy Exposure Study is to monitor planned and unplanned pregnancies exposed to benralizumab for the treatment of asthma and to evaluate the possible teratogenic effect of this medication relative to the primary pregnancy outcome of major birth defects and the secondary pregnancy outcomes of preterm delivery, small for gestational age (SGA) infants, spontaneous abortion, stillbirth, elective termination, and small for age for postnatal growth. The lack of human fetal safety data for benralizumab from a controlled clinical study makes such a monitoring system an important component of epidemiologic research on the safety of this drug.

Information regarding the safety of benralizumab in human pregnancy is essential from a public health perspective as inadvertent pregnancy exposure to benralizumab may take place, and safety information for women who may need this medication is necessary to inform clinical practice. This is a prospective observational study of pregnant women exposed to benralizumab to evaluate fetal, infant, and childhood outcomes and their live born offspring through the first year of life to estimate incidence rates for the potential safety signals of adverse pregnancy outcomes, embryo-fetal growth and development, and adverse infant outcomes.

2 STUDY OBJECTIVES

The primary objective of the study is to estimate the overall rate of major structural defects, as well as to evaluate any pattern of anomalies, in infants of women diagnosed with asthma exposed to benralizumab during pregnancy compared to infants of women with a diagnosis of asthma who have used a medication other than benralizumab for the treatment of their disease, and to infants of women who do not have a diagnosis of asthma and who have not used benralizumab during pregnancy.

The secondary objectives are to estimate the rate of study outcomes (other than major structural defects) in women with asthma exposed to benralizumab during pregnancy. These secondary objectives, where numbers permit, include determination of an increase in the risk of spontaneous abortion, stillbirth, elective termination, or preterm delivery in benralizumab-exposed pregnancies compared to disease-matched unexposed pregnancies, and among live born infants, to determine if there is an increase in the risk of reduced birth size, postnatal growth deficiency up to one year of age, in benralizumab-exposed pregnancies compared to the primary comparison group of disease-matched unexposed pregnancies. Additional secondary objectives of the study are to compare the risk for each of the specified outcomes in benralizumab-exposed pregnancies to a secondary comparison group of healthy women who have no diagnosis of asthma, have not had exposure to a known human teratogen, and have not taken benralizumab in pregnancy.

3 STUDY DESIGN AND POPULATION

This is a prospective, observational, exposure cohort study of pregnancy outcomes in women who have been diagnosed with asthma, and who have been exposed to benralizumab during pregnancy or within 8 weeks of the first day of the last menstrual period (LMP), compared to pregnancy outcomes in women with asthma who have not been exposed to benralizumab during pregnancy (disease-matched comparison group), and pregnancy outcomes in women not diagnosed with asthma (non-disease-matched comparison group) who have not been exposed to benralizumab during pregnancy.

The cohort study will be conducted by investigators at the University of California Research Center for the Organization of Teratology Information Specialists (OTIS). OTIS is a network of university and health department based telephone information centers serving pregnant women and health care providers throughout North America.

Inclusion Criteria:

(1) Cohort 1: Benralizumab-Exposed

- Eligible subjects will be currently pregnant women diagnosed with asthma who contact the OTIS Research Center and who have been exposed to beralizumab for any number of days, at any dose, and at any time from 8 weeks before the first day of the LMP up to and including the end of pregnancy.

- Eligible subjects will be currently pregnant women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

(2) Cohort 2: Treated Comparison Group

- Eligible subjects will be currently pregnant women diagnosed with asthma and who are exposed to asthma medications for any number of days, at any dose, and at any time from the first day of the LMP up to the date of enrolment, who contact the OTIS Research Center but who were not exposed to benralizumab during pregnancy or within 8 weeks prior to the first day of the LMP.

- Eligible subjects will be currently pregnant women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

(3) Cohort 3: Non-Asthmatic Comparison

- Eligible subjects will be currently pregnant women who contact the OTIS Research Center who may potentially have been exposed to non-teratogenic agents during this time period.

- Eligible subjects will be currently pregnant women who agree to the conditions and requirements of the study including the interview schedule and release of medical records.

Exclusion Criteria:

(1) Cohort 1: Benralizumab-Exposed

- Women who have had exposure to another biologic, used for any indication, anytime during pregnancy or within 8 weeks of LMP.
- Women will not be eligible for Cohort 1 if they first contact the OTIS Research Center after prenatal diagnosis of a major birth defect.
- Retrospective cases (outcome of pregnancy known prior to enrollment).
- Women will not be eligible for Cohort 1 if they have enrolled in the current study with a previous pregnancy.

(2) Cohort 2: Treated Disease Comparison

- Women with exposure to benralizumab any time during pregnancy or within 8 weeks prior to LMP.
- Women will not be eligible for Cohort 2 if they first come in contact with the OTIS Research Center after prenatal diagnosis of a major birth defect.
- Retrospective cases (outcome of pregnancy known prior to enrollment).
- Women will not be eligible for Cohort 2 who have enrolled in the current study with a previous pregnancy.

(3) Cohort 3: Non-Asthmatic Comparison

- Women who have been exposed to any known teratogenic agents as determined by the OTIS Research Center (list in Appendix 1) for any number of days, at any dose, from the first day of the last menstrual period up to and including the end of pregnancy.
- Women will not be eligible for Cohort 3 if they have a current self-reported diagnosis of asthma, current or previous.
- Women will not be eligible for Cohort 3 if they come in contact with the OTIS Research Center after prenatal diagnosis of a major birth defect.
- Retrospective cases (outcome of pregnancy known prior to enrollment).
- Women will not be eligible for Cohort 3 if they have enrolled in the current study with a previous pregnancy.

4 STUDY INITIATION AND PROTOCOL RECRUITMENT SAMPLE SIZE

The Benralizumab Pregnancy Exposure Study was initiated in March 12, 2019. The first subject was recruited in March 2019 . In the start-up year of the Registry, a plan to raise awareness about the study (see Appendix I) specifically designed to improve identification of exposed pregnancies while enhancing recruitment of appropriate controls was developed and implemented. The overall protocol recruitment sample size for the cohort study is 200 participants in the benralizumab-exposed group and 300 participants each in the comparison cohort groups who reside in the U.S. and Canada.

5 REFERRAL SOURCES AND RECRUITMENT

Recruitment of eligible subjects is accomplished through recruitment efforts through OTIS member services, scientific meetings, direct mail to healthcare providers, journal advertising, internet advertising, and referrals from the Sponsor. The number of subjects enrolled by disease group and sources of referrals through August 15, 2019, are summarized in Table 5.1.

Table 5.1. Recruitment and Referral Source for All Enrolled Subjects

	Benralizumab-Exposed Prospective Cohort	Diseased Unexposed	Non-Diseased Unexposed
Recruitment Goal	200	300	300
Enrolled Subjects	1	15	6
Referral Source Available	1	14	6
Sponsor	0	0	0
Health-care Professional	1	2	0
UC Rely[a]	0	0	1
Internet	0	10	5
Patient Support Group	0	0	0
OTIS Member Service	0	2	0
Other	0	0	0

[a]UC Rely is a consortium of obstetric groups at 4 of the University of California (UC) medical centers

6 REGISTRY AWARENESS ACTIVITIES

Specific awareness activities since study start are summarized in Appendix I.

7 STUDY PROGRESS AND RECRUITMENT

Study progress from start-up through 5 months, encompassing March 12, 2019 to August 15, 2019, is presented in this report.

8 SUBJECTS ENROLLED IN THE COHORT STUDY WITH PREGNANCY OUTCOME

All subjects enrolled in the cohort study with outcomes reported between March 12, 2019 to August 15, 2019 are shown by exposure in Table 8.1. In Section 8 tables, % = (n/N) * 100; N is the number of subjects enrolled in the cohort, and "n" represents the number with the event described in the row heading (numerator).

Table 8.1. Enrolled Subjects with Pregnancy Outcome

	Benralizumab-Exposed (N = 1) n(%)	Diseased Unexposed (N = 15) n(%)	Non-Diseased Unexposed (N = 6) n(%)	Total Enrolled (N = 22) n(%)
Number of Pregnant Women with Outcome	0	2 (13.3)	0	2 (9.1)

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

9 DEMOGRAPHIC AND BASELINE CHARACTERISTICS FOR ENROLLED SUBJECTS WITH PREGNANCY OUTCOME

Demographic and baseline characteristics for all subjects with a known pregnancy outcome reported between March 12, 2019 to August 15, 2019 are shown by study cohort in Tables 9.1 to 9.25. In Section 9 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 9.1. Maternal Age (Years) at Due Date - Continuous

Age (years)	Benralizumab-Exposed (N = 0)	Diseased Unexposed (N = 2)	Non-Diseased Unexposed (N = 0)
Mean	----	29.8	----
Standard Deviation	----	7.9	----
Minimum	----	24.2	----
Maximum	----	35.4	----
Median	----	29.8	----
1st quartile	----	27.0	----
3rd quartile	----	32.6	----

N: Number of subjects with pregnancy outcome

Table 9.2. Maternal Age at Due Date - Categorical

Age Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
<25 years	0	1 (50.0)	0
25-29 years	0	0	0
30-34 years	0	0	0
>34 years	0	1 (50.0)	0

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

Table 9.3a. Maternal Ethnicity

Ethnicity Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Non-Hispanic	0	2 (100.0)	0
Hispanic	0	0	0

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

Table 9.3b. Maternal Race

Race Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
White	0	2 (100.0)	0
Black	0	0	0
Asian/Pacific Islander	0	0	0
Native American	0	0	0
Other	0	0	0

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

Table 9.4a. Paternal Ethnicity

Ethnicity Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Non-Hispanic	0	2 (100.0)	0
Hispanic	0	0	0

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

Table 9.4b. Paternal Race

Race Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
White	0	2 (100.0)	0
Black	0	0	0
Asian/Pacific Islander	0	0	0
Native American	0	0	0
Other	0	0	0

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

Table 9.5. Maternal Educational Category

Years of Completed Education	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
<12 years	0	0	0
12-15 years	0	0	0
>15 years	0	2 (100.0)	0

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

Table 9.6. Yearly Household Income

Yearly Household Income Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
<$10,000	0	0	0
$10,000 - $50,000	0	0	0
≥$50,000	0	2 (100.0)	0

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

Table 9.7. Hollingshead Socioeconomic Category[a]

Hollingshead Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
1	0	0	0
2	0	2 (100.0)	0
3	0	0	0
4	0	0	0
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 9.8. Maternal Pre-Pregnancy Body Mass Index (BMI)[a]

BMI Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
<18.5 (underweight)	0	0	0
18.5-24.9 (normal weight)	0	1 (50.0)	0
25-29.9 (overweight)	0	1 (50.0)	0
≥30 (obese)	0	0	0

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

Table 9.9. Gravidity at Time of Enrollment

Number of Times Ever Pregnant[a]	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
1	0	0	0
2-3	0	1 (50.0)	0
4-5	0	1 (50.0)	0
≥6	0	0	0

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

Table 9.10. Parity at Time of Enrollment

Number of Previous Live Birth or Stillbirth Deliveries	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
0	0	0	0
1-2	0	2 (100.0)	0
3-4	0	0	0
≥5	0	0	0

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

Table 9.11. Previous Spontaneous Abortions at Time of Enrollment [a]

Number of Previous Pregnancies Ending in Spontaneous Abortion	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
0	0	1 (50.0)	0
1	0	0	0
2	0	0	0
≥3	0	1 (50.0)	0

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

Table 9.12. Previous Elective Terminations at Time of Enrollment

Number of Previous Pregnancies Ending in Elective Termination	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
0	0	2 (100.0)	0
1	0	0	0
2	0	0	0
≥3	0	0	0

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

Table 9.13. Gestational Age (Weeks) of Pregnancy at Time of Enrollment - Continuous

Weeks' Gestation	Benralizumab-Exposed (N = 0)	Diseased Unexposed (N = 2)	Non-Diseased Unexposed (N = 0)
Mean	----	22.2	----
Standard Deviation	----	19.1	----
Minimum	----	8.7	----
Maximum	----	35.7	----
Median	----	22.2	----
1st quartile	----	15.5	----
3rd quartile	----	29.0	----

N: Number of subjects with pregnancy outcome

Table 9.14. Gestational Age of Pregnancy at Time of Enrollment - Categorical

Weeks' Gestation Category	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
<13 weeks	0	1 (50.0)	0
13-19.9 weeks	0	0	0
≥20 weeks	0	1 (50.0)	0

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

Table 9.15. Geographic Area of Residence

Country	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
U.S.	0	2 (100.0)	0
Canada	0	0	0

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

Table 9.16a. Asthma Symptom Control Test Over Previous Month Among Asthmatics by Medication Group

	Intake Score 1 or 2		Intake #2[b] Score 1 or 2		20 weeks Score 1 or 2		32 weeks Score 1 or 2		Postpartum Score 1 or 2	
Symptom	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)
Interfered[a]	----	1/2 (50.0)	----	0/1 (0.0)	----	----	----	----	----	0/1 (0.0)
Short breath[a]	----	1/2 (50.0)	----	0/1 (0.0)	----	----	----	----	----	0/1 (0.0)
Up at night[a]	----	1/2 (50.0)	----	0/1 (0.0)	----	----	----	----	----	0/1 (0.0)
Rescue med[a]	----	1/2 (50.0)	----	0/1 (0.0)	----	----	----	----	----	0/1 (0.0)
Overall rating more severe[a]	----	1/2 (50.0)	----	0/1 (0.0)	----	----	----	----	----	0/1 (0.0)
Total score <20, not well controlled	----	1/2 (50.0)	----	0/1 (0.0)	----	----	----	----	----	0/1 (0.0)

[a]Likert Scale 1-5; a score of 1-2 indicates more severe.

[b]Intake #2 administered when subjects enroll 12-20 weeks. The subject is asked to answer questions for 4-8 weeks gestation.

N: Number of subjects with pregnancy outcome

% = (n/N') * 100 for each category of test. N': Number of subjects with pregnancy outcome with available information.

9.16b. Exacerbations since Previous Interview Among Asthmatics by Medication Group

	Intake		20 weeks		32 weeks		Postpartum	
	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)
Hospitalized overnight	----	0/2 (0.0)	----	----	----	----	----	0/1 (0.0)
ER visit	----	1/2 (50.0)	----	----	----	----	----	0/1 (0.0)
If yes, Steroid - yes	----	0/1 (0.0)	----	----	----	----	----	----
Unscheduled MD visit	----	0/2 (0.0)	----	----	----	----	----	0/1 (0.0)
If yes, Steroid - yes	----	----	----	----	----	----	----	----
Oral steroid use	----	0/2 (0.0)	----	----	----	----	----	0/1 (0.0)
Any exacerbation (any of the above)	----	1/2 (50.0)	----	----	----	----	----	0/1 (0.0)

N: Number of subjects with pregnancy outcome

% = (n/N') * 100 for each category of test. N': Number of subjects with pregnancy outcome with available information.

9.16c. Medication Use Previous Month among Asthmatics by Medication Group

	Intake		20 weeks		32 weeks		Postpartum	
	Benralizumab -Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab -Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab -Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)
Using medication less than prescribed - yes	----	1/2 (50.0)	----	----	----	----	----	1/1 (100.0)
Quit	----	1/1 (100.0)	----	----	----	----	----	----
Reduce	----	0/1 (0.0)	----	----	----	----	----	----
Reason								
Pregnancy	----	0/1 (0.0)	----	----	----	----	----	0/1 (0.0)
Feel better	----	1/1 (100.0)	----	----	----	----	----	1/1 (100.0)
Other	----	0/1 (0.0)	----	----	----	----	----	0/1 (0.0)

N: Number of subjects with pregnancy outcome

% = (n/N') * 100 for each category of test. N': Number of subjects with pregnancy outcome with available information.

Table 9.17. Prenatal, Multivitamin or Folic Acid Supplement Use and Timing in Pregnancy

Timing of Vitamin Use	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Began prior to conception	0	2 (100.0)	0
Post-conception only	0	0	0
Have not taken at all	0	0	0

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

Table 9.18. Alcohol Use in Pregnancy

Any Alcohol in Pregnancy (post-conception)	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Yes	0	0	0

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

Table 9.19. Tobacco Use in Pregnancy

Any Tobacco Smoked in Pregnancy (post-conception)	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Yes	0	0	0

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

Table 9.20. Exposure to Major Known or Suspected Human Teratogens

Major Known or Suspected Human Teratogens in Pregnancy (post- conception)	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Yes	0	0	0

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

Table 9.21. Dose treatment used between LMP and Pregnancy Outcome (1st treatment dose if multiple doses occurred)

Dose and Frequency of Benralizumab	Benralizumab-Exposed (N = 0) n(%)
30 mg every 4 weeks	0
30 mg every 8 weeks	0

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

Table 9.22. Gestational Timing of Benralizumab Use in Pregnancy

Total Number of Weeks Post-Conception of Medication Use in Pregnancy[a]	Benralizumab-Exposed (N = 0) n(%)
8 weeks prior to LMP 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	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. For this table, the 1st trimester will include LMP to DOC, i.e. if a subject is exposed in between LMP to DOC and in the 1st trimester, she will be categorized as having exposure in the 1st Trimester.
[b]Last dose occurred in [LMP, DOC)

Table 9.23. GINA Classification during Pregnancy

	Last Menstrual Period (LMP) or First Medication after LMP		32 weeks	
GINA Step Classification[a, b]	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)
1	----	1/2 (50.0)	----	----
2	----	0/2 (0.0)	----	----
3	----	0/2 (0.0)	----	----
4	----	1/2 (50.0)	----	----
5	----	0/2 (0.0)	----	----
Unable to Classify	----	0/2 (0.0)	----	----

[a]Global initiative for asthma (GINA) classification is based on maternal report, and confirmed by medical records. In some cases, medical records are required to classify.
[b]Possible score 1-5 with higher score indicating more severe disease.
N: Number of subjects with pregnancy outcome.
% = (n/N) * 100; N': Number of subjects with GINA information available.

Table 9.24. Prenatal Diagnostic Tests Performed Anytime During Pregnancy

	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Ultrasound Level 1	0	2 (100.0)	0
Ultrasound Level 2	0	1 (50.0)	0
Chorionic villus sampling (CVS)	0	0	0
Amniocentesis	0	0	0

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

Table 9.25. Prenatal Diagnostic Tests Performed Prior to Enrollment

	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 2) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Ultrasound Level 1	0	2 (100.0)	0
Ultrasound Level 2	0	1 (50.0)	0
Chorionic villus sampling (CVS)	0	0	0
Amniocentesis	0	0	0

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

10 PREGNANCY OUTCOMES IN WOMEN ENROLLED IN THE COHORT STUDY

Pregnancy outcome information for all subjects reported between March 12, 2019 and August 15, 2019 shown by study cohort in Tables 10.1 to 10.12. N is those with outcome, " N' " is those in the overall sample that are eligible for an outcome being described, N'' represents the number of cases with data available for an outcome that is specific to the events that are being described in that table (i.e., is the denominator for those events), and "n" represents the number with that event (numerator).

Table 10.1. Pregnancy Outcome

	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=2) n/N'(%)	Non-Diseased Unexposed (N=0) n/N'(%)
Live birth	----	1/2 (50.0)	----
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	----	0/1 (0.0)	----
Spontaneous Abortion (SAB)	----	1/2	----
Spontaneous Abortion-Twins	----	0/1	----
Stillbirth	----	0/2 (0.0)	----
Termination	----	0/2 (0.0)	----
Social	----	----	----
Medical	----	----	----
Lost to Follow Up (LTFU)	----	0/2 (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.

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

	Benralizumab-Exposed (N = 0) n(%)	Diseased Unexposed (N = 1) n(%)	Non-Diseased Unexposed (N = 0) n(%)
Number of SAB Events (n)[a]	0	1	0
Left Truncation Accounted SAB Rate [b]	0	100%	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 Kaplan-Meier estimate at 20 weeks' gestation, accounting for left truncation because women can enroll at various times in gestation.
N: Number of subjects with outcome enrolled and exposed prior to 20 weeks' gestation and with follow up.

Table 10.3. Major Birth Defects

	Benralizumab-Exposed n/N(%)	Diseased Unexposed 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)	----
Number of all pregnancies (excluding LTFU) with major birth defects	----	0/2 (0.0)	----

A pregnancy with multiple births is counted as one malformed outcome if any one or more infants/fetuses are malformed.
% = (n/N) * 100

10.3a Major Birth Defects among Pregnancies with Multiple Births

	Benralizumab-Exposed n/N(%)	Diseased Unexposed n/N(%)	Non-Diseased 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.
% = (n/N) * 100

Table 10.4. Major Birth Defects in Live Born Infants Compared to Population Reference

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

[a]MACDP (Metropolitan Atlanta Congenital Defects Program). 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.
% = (n/N) * 100

Table 10.5. Preterm Delivery (PTD) 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)

	Benralizumab-Exposed (N = 0)	Diseased Unexposed (N = 1)	Non-Diseased Unexposed (N = 0)
Number of PTD (n)	0	0	0
Left Truncation Accounted PTD Rate[a]	0	0	0

[a]Computed using Kaplan-Meier estimate at 37 weeks' gestation, accounting for left truncation due to varying time in gestation at enrollment.
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 10.6. Gestational Age (Weeks) At Delivery among Pregnancies Ending in Live Birth (Multiple Births Excluded)

	Benralizumab-Exposed (N = 0)	Diseased Unexposed (N = 1)	Non-Diseased Unexposed (N = 0)
Mean	----	40.3	----
Standard Deviation	----	----	----
Minimum	----	40.3	----
Maximum	----	40.3	----
Median	----	40.3	----
1st quartile	----	40.3	----
3rd quartile	----	40.3	----

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

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

	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=1) n/N'(%)	Non-Diseased Unexposed (N=0) 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 10.8. Birth Size for Full Term Infants (Multiple Births Excluded)

	Benralizumab-Exposed (N = 0)	Diseased Unexposed (N = 1)	Non-Diseased Unexposed (N = 0)
Birth Weight - grams	N'= 0	N'= 1	N'= 0
Mean	----	3288.5	----
Standard deviation	----	----	----
Minimum	----	3288.5	----
Maximum	----	3288.5	----
Median	----	3288.5	----
1st quartile	----	3288.5	----
3rd quartile	----	3288.5	----
Birth Length - cm	N'= 0	N'= 1	N'= 0
Mean	----	52.1	----
Standard deviation	----	----	----
Minimum	----	52.1	----
Maximum	----	52.1	----
Median	----	52.1	----
1st quartile	----	52.1	----
3rd quartile	----	52.1	----
Birth Head Circumference - cm	N'= 0	N'= 0	N'= 0
Mean	----	----	----
Standard deviation	----	----	----
Minimum	----	----	----
Maximum	----	----	----
Median	----	----	----
1st quartile	----	----	----
3rd quartile	----	----	----

N: Number of single pregnancies resulting in at least one full term infant
N': at each category of growth measurement: Number of subjects enrolled with live birth outcome and for whom the specific growth measurement is available.

Table 10.9. Small for Gestational Age (SGA) at Birth Among Live Born Infants (Multiple Pregnancies Excluded)[a]

	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=1) n/N'(%)	Non-Diseased Unexposed (N=0) n/N'(%)
Weight	----	0/1 (0.0)	----
Length	----	0/1 (0.0)	----
Head Circumference	----	----	----
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': Number of live born infants with growth measurement available.

Table 10.10. Postnatal Growth Percentile at One Year - Continuous (Multiple Births Excluded)

	Benralizumab-Exposed (N = 0)	Diseased Unexposed (N = 0)	Non-Diseased Unexposed (N = 0)
Weight - percentile	N'= 0	N'= 0	N'= 0
Mean	----	----	----
Standard deviation	----	----	----
Minimum	----	----	----
Maximum	----	----	----
Median	----	----	----
1st quartile	----	----	----
3rd quartile	----	----	----
Length - percentile	N'= 0	N'= 0	N'= 0
Mean	----	----	----
Standard deviation	----	----	----
Minimum	----	----	----
Maximum	----	----	----
Median	----	----	----
1st quartile	----	----	----
3rd quartile	----	----	----
Head Circumference - percentile	N'= 0	N'= 0	N'= 0
Mean	----	----	----
Standard deviation	----	----	----
Minimum	----	----	----
Maximum	----	----	----
Median	----	----	----
1st quartile	----	----	----
3rd quartile	----	----	----

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 10.11. Postnatal Growth One Year - Percentile ≤10th (Multiple Births Excluded)

	Benralizumab-Exposed (N = 0)	Diseased Unexposed (N = 0)	Non-Diseased Unexposed (N = 0)
Weight ≤ 10th centile[a]	----	----	----
Length ≤ 10th centile[a]	----	----	----
Head 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 10.12. Postnatal Events - Hospitalizations in Infants up to One Year of Age (Including Infants from Multiple Births)

	Benralizumab-Exposed (N=0) n/N'(%)	Diseased Unexposed (N=1) n/N'(%)	Non-Diseased Unexposed (N=0) n/N'(%)
Yes	----	0/1 (0.0)	----

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

11 LINE LISTINGS FOR STUDY OUTCOME VARIABLES – MAJOR MALFORMATION, PATTERN OF MINOR MALFORMATIONS AND NEONATAL DEATH

11.1. Major Malformations by Cohort –

Listing 1. Major Malformations for Benralizumab-Exposed Group - None

Pregnancy ID	Outcome ID	ICD9 Code	Malformation	Mat Age	Race	Multiple Birth	Birth outcome	Dose

Listing 2. Major Malformations for Diseased Unexposed Group - None

Pregnancy ID	Outcome ID	ICD9 Code	Malformation	Mat Age	Race	Multiple Birth	Birth outcome

Listing 3. Major Malformations for Non-Diseased Unexposed Group - None

Pregnancy ID	Outcome ID	ICD9 Code	Malformation	Mat Age	Race	Multiple Birth	Birth outcome

11.2. Neonatal or Infant Death anytime by Cohort

Listing 4. Neonatal or Infant Death – Benralizumab-Exposed Group - None

Pregnancy ID	Outcome ID	Age at Death	Notes

Listing 5. Neonatal or Infant Death – Diseased Unexposed Group - None

Pregnancy ID	Outcome ID	Age at Death	Notes

Listing 6. Neonatal or Infant Death – Non-Diseased Unexposed Group - None

Pregnancy ID	Outcome ID	Age at Death	Notes

11.3. Hospitalizations in Infants up to One Year of Age by Cohort

Listing 7. Hospitalizations – Benralizumab-Exposed Group - None

Pregnancy ID	Outcome ID	Age at Event	Notes

Listing 8. Hospitalizations – Diseased Unexposed Group - None

Pregnancy ID	Outcome ID	Age at Event	Notes

Listing 9. Hospitalizations – Non-Diseased Unexposed Group - None

Pregnancy ID	Outcome ID	Age at Event	Notes

12 PRELIMINARY CONCLUSIONS

The Advisory Board met on November 7, 2019 in Washington, DC. During the meeting, the board reviewed results from a survey sent by AAAAI to selected member clinicians to determine use and comfort with prescribing biologics for the treatment of asthma during pregnancy. The results presented indicated that biologics are not frequently used to treat pregnant women with asthma. Based on the limited number of women enrolled in the Benralizumab Pregnancy Exposure Registry, no conclusions about the safety of benralizumab in pregnancy can be made at this time.

Appendix I - Fasenra® Recruitment Summary

Outreach Efforts in Year 1

March – September 2019

Communication with OTIS Network Members

On June 24, 2019, OTIS held their Annual Education Meeting in San Diego, CA. Recruitment goals and methods to enhance recruitment were discussed. Throughout the year, study leads also have regular communication with the research coordinators at each TIS site in order to update the coordinators with important information and continue to encourage study referrals.

Digital and Online Advertising

1. Facebook ads specific to asthma and pregnancy, as well as Fasenra® and pregnancy, began running on March 13,2019 and continued during the reporting period. **Paid ads on social media are posts that require payment to distribute to larger or more specific audiences.*
2. Organic Facebook and Twitter social media posts promoting the study were posted monthly on OTIS/MotherToBaby National's pages. Additional posts were placed on our local TIS affiliate, MotherToBaby California's, social media accounts. **Organic posts are any posts that are un-paid, typically distributed to people who are already following our content or who see our shares, likes, etc.*
3. Information about the study was added to the OTIS/MotherToBaby website, which accepts both self-referrals from potential participants and health care provider-initiated patient referrals.
4. OTIS/MotherToBaby's app includes information about the study and links the user to a sign-up form. Available for both iOS and Android devices, the app includes a clear pathway for health care providers to refer patients.
5. The study is listed on the FDA Pregnancy Registry website under "Asthma."
6. OTIS submitted the registry listing application on the FDA Pregnancy Registry website under "Fasenra®." This is currently awaiting approval.

Contact with Healthcare Professionals

UC Rely

Referrals are received from UC Rely, a consortium between four University of California Medical Campuses. A coordinator within the Obstetrics Department at each campus screens pregnant women who are potentially eligible for OTIS Studies and, if the woman agrees, she is referred to our coordinating center at UCSD. At the request of our UC Rely partners, we created a patient-oriented FAQs document that could be provided to potential participants at each UC Rely site. In addition, one of the campuses (UCSF) runs digital ads for OTIS Studies in their patient waiting areas.

Social Media

Posts promoting the study are schedule regularly on the MotherToBaby SERMO page. SERMO is a popular social networking platform for health care providers. It is private, exclusively for physicians and functions similar to other social media accounts.

Scientific Meetings and Presentations

OTIS Studies staff attended and exhibited at professional scientific meetings for relevant provider groups, including but not limited to obstetrics, maternal-fetal medicine, allergy and immunology, and internal medicine/primary care. All leads obtained at conferences were sent additional information on the study, how to refer, and additional resources for their patients (see *Email Marketing*, below).

Meetings that we attended during the reporting period are listed chronologically below:

MEETING	DATE
American Pharmacists Association (APhA)	March 2019
American College of Obstetricians and Gynecologists (ACOG)	May 2019
American College of Nurse Midwives (ACNM)	May 2019
Primed West	May 2019

Email Marketing

In March and April 2019, OTIS sent emails announcing study to over 2,500 relevant HCP contacts which included Allergists & Immunologists, OB/GYNs, MFMs, Nurse-Midwives, Pharmacists, Primary Care and others. The email outlined study goals, participant eligibility and encouraged referrals.

All health care provider contacts obtained at conferences and professional meetings were sent a post-conference follow-up email communication, which included study and referral information linked to pages on the MotherToBaby website and other relevant resources (e.g., fact sheets, ordering promotional materials). These contacts were then added to OTIS' electronic newsletter listserv, which is sent out quarterly and highlights the studies, encourages referrals, and announces new relevant resources and brochures/materials that are available to order.

In May 2019, for ACOG exhibit booth promotion, we sent an email blast to both pre-registered attendees and our existing relevant health care provider contacts. The email contained a dedicated landing page for tracking health care provider engagement. These emails and landing page highlighted our attendance at the upcoming meeting, invited attendees to visit our both for resources and to learn about our studies, and invited the provider to sign up for our listserv to receive future email communications, including study updates.

Strategic Partnerships

Allergy & Asthma Network

Information about the study and links are listed on the Allergy & Asthma Network's Asthma & Pregnancy page.

Society of Maternal-Fetal Medicine (SMFM)

SMFM includes lists of newly added/updated OTIS/MotherToBaby fact sheets in their monthly e-newsletter.

Mamas Facing Forward

Mamas Facing Forward is a website that serves as a database of useful resources for moms and moms-to-be who are dealing with chronic illnesses. OTIS/MotherToBaby is listed as a resource and has a featured page on their website under pregnancy resources. In March 2019, Mamas Facing Forward creator, Mariah Leach, co-wrote a blog with OTIS, detailing her pregnancy studies participation from the perspective as a current participant. In April 2019, OTIS/MotherToBaby organized a Facebook Live event with Mariah to promote the blog and encourage pregnancy study participation.

TheMighty

MotherToBaby established a partner profile page on this organization's site directing their members who indicate an interest regarding multiple sclerosis to more information on the OTIS study.

National Organization for Rare Diseases (NORD)

MotherToBaby is listed on the National Organization for Rare Diseases (NORD) website as a patient organization and resource.

PatientsLikeMe

OTIS/MotherToBaby has an ongoing partnership with PatientsLikeMe, an organization for patients with various diseases to connect with each other and learn about research studies. PLM posts relevant MotherToBaby blogs and other resources in patient forums.

Coherent RX

Coherent RX runs The Patient Education Genius, which is an app that gives clinicians one access point for evidence-based patient education resources. All OTIS online resources are included in their library of patient educational resources.

Study Promotional Materials

New Promotional Items – Referral Tear Pads & StickyCleans

In April 2019, OTIS created tailored tear pads for each specialty group (General, Asthma) that function as referral sheets and note pads. These items will be available for order on the OTIS website and distributed at professional meetings/conferences.

OTIS also created branded microfiber self-adhesive cloths called StickyCleans. These promotional items are intended for cleaning various screens (mobile devices, computers, laptops, etc.) and lenses and can stick to any desired surface. Each cloth contains the OTIS phone number, studies URL, and are packaged with a referral card for additional information. These items are distributed at our booth at professional meetings/conferences.

Brochures and Business Cards

Health care provider brochures, study inserts and referral cards are available for allergists, immunologists, obstetricians, maternal-fetal specialists and other healthcare provider groups. Patient-oriented materials are also available. Brochures are available at all promotional events and used extensively in mailed communications; they are also available to order online on the MotherToBaby website.

OTIS Fact Sheets

In September 2019, the OTIS education committee finalized the "Benralizumab (Fasenra®) in Pregnancy" Fact Sheet. Along with the "Asthma in Pregnancy" Fact Sheet, both are available on the MotherToBaby website and include a blurb about the study. Other relevant fact sheets that include information about the asthma and pregnancy study are: inhaled corticosteroids, albuterol, formoterol, salmeterol, montelukast, and prednisone/prednisolone. Fact sheets are available for free download on the website, mailed and/or email to healthcare providers, and print versions are available at our booth at scientific meetings. The OTIS Education Committee will continue to update the fact sheets when new and relevant information has been published.

AAAAI Efforts

Our partners at AAAAI engaged in a variety of efforts to promote the study and encourage patient referrals and/or self-enrollment. These include:

- Advertisements promoting the study were placed in the AAAAI journals periodically (as space became available) during the reporting period.
- The Feb/Mar 2019 issue of Practice Matters, a bi-weekly newsletter to AAAAI members, included information on the VAMPSS study.
- An email was sent on May 15, 2019 to all AAAAI members on "New FDA Draft Guidance on Post-approval Pregnancy Safety Studies Recognizes VAMPSS".

Sponsor Activities

MSL Communications

In March 2019, OTIS provided the sponsor with communication toolkits for their medical science liaisons (MSLs) and for healthcare providers with whom the sponsor has contact. In August 2019, OTIS developed an additional flyer/handout for study promotion at the Sponsor's request.

Transfer of Callers to OTIS

Warm transfer of callers is under discussion with AstraZeneca.

US & Canadian Active Prescriber Lists

AstraZeneca is discussing possibility of releasing top prescriber list to OTIS.

Appendix II – Literature

No published studies in the past year pertaining to benralizumab and pregnancy outcome