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

2021 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 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 . A marketing plan was developed to raise awareness about the study (see Appendix I) and 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. The protocol outlines the probability of observing rate ratios in excess of different thresholds either by chance, or when there is a true underlying increase in risk, given the planned sample size.

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, 2021, 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	9	116	52
Referral Source			
Sponsor	1	0	0
Health-care Professional	7	11	4
UC Rely[a]	0	3	1
Internet	1	88	43
Patient Support Group	0	1	0
OTIS Member Service	0	7	2
Other	0	6	2

[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 2 years 5 months, encompassing March 12, 2019 to August 15, 2021, 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, 2021 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 of participants with the event described in the row heading (numerator).

Table 8.1. Enrolled Subjects with Pregnancy Outcome

	Benralizumab-Exposed (N = 9) n(%)	Diseased Unexposed (N = 116) n(%)	Non-Diseased Unexposed (N = 52) n(%)	Total Enrolled (N = 177) n(%)
Number of Pregnant Women with Outcome	3 (33.3)	83 (71.6)	27 (51.9)	113 (63.8)

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, 2021 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 = 3)	Diseased Unexposed (N = 83)	Non-Diseased Unexposed (N = 27)
Mean	35.7	32.2	33.1
Standard Deviation	1.6	4.8	4.4
Minimum	33.9	21.6	24.0
1st quartile	35.0	28.1	30.2
Median	36.2	32.1	33.6
3rd quartile	36.5	35.3	36.2
Maximum	36.9	43.2	42.6

N: Number of subjects with pregnancy outcome

Table 9.2. Maternal Age at Due Date - Categorical

Age Category	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
<25 years	0	3 (3.6)	2 (7.4)
25-29 years	0	26 (31.3)	5 (18.5)
30-34 years	1 (33.3)	28 (33.7)	7 (25.9)
>34 years	2 (66.7)	26 (31.3)	13 (48.1)

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

Table 9.3a. Maternal Ethnicity

Ethnicity Category	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Non-Hispanic	3 (100.0)	70 (84.3)	25 (92.6)
Hispanic	0	13 (15.7)	2 (7.4)

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

Table 9.3b. Maternal Race

Race Category	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Data Available	3 (100.0)	82 (98.8)	27 (100.0)
White	2 (66.7)	72 (87.8)	21 (77.8)
Black	0	2 (2.4)	3 (11.1)
Asian/Pacific Islander	1 (33.3)	4 (4.9)	2 (7.4)
Native American	0	1 (1.2)	0
Other	0	3 (3.7)	1 (3.7)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100 for the first row; for the other rows, % = n/number of subjects with information available.

Table 9.4a. Paternal Ethnicity

Ethnicity Category	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Data Available	3 (100.0)	80 (96.4)	27 (100.0)
Non-Hispanic	3 (100.0)	70 (87.5)	23 (85.2)
Hispanic	0	10 (12.5)	4 (14.8)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100 for the first row; for the other rows, % = n/number of subjects with information available.

Table 9.4b. Paternal Race

Race Category	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Data Available	3 (100.0)	81 (97.6)	27 (100.0)
White	2 (66.7)	67 (82.7)	20 (74.1)
Black	0	7 (8.6)	3 (11.1)
Asian/Pacific Islander	1 (33.3)	4 (4.9)	2 (7.4)
Native American	0	2 (2.5)	0
Other	0	1 (1.2)	2 (7.4)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100 for the first row; for the other rows, % = n/number of subjects with information available.

Table 9.5. Maternal Educational Category

Years of Completed Education	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
<12 years	0	1 (1.2)	0
12-15 years	0	18 (21.7)	4 (14.8)
>15 years	3 (100.0)	64 (77.1)	23 (85.2)

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

Table 9.6. Yearly Household Income

Yearly Household Income Category	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Data Available	2 (66.7)	76 (91.6)	24 (88.9)
<$10,000	0	5 (6.6)	1 (4.2)
$10,000 - $50,000	0	12 (15.8)	3 (12.5)
>=$50,000	2 (100.0)	59 (77.6)	20 (83.3)

N: Number of subjects with pregnancy outcome
% = (n/N) * 100 for the first row; for the other rows, % = n/number of subjects with information available.

Table 9.7. Hollingshead Socioeconomic Category[a]

Hollingshead Category	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Data Available	3 (100.0)	82 (98.8)	27 (100.0)
1	2 (66.7)	31 (37.8)	11 (40.7)
2	1 (33.3)	34 (41.5)	9 (33.3)
3	0	15 (18.3)	3 (11.1)
4	0	1 (1.2)	3 (11.1)
5	0	1 (1.2)	1 (3.7)

[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 for the first row; for the other rows, % = n/number of subjects with information available.

Table 9.8. Maternal Pre-Pregnancy Body Mass Index (BMI)[a]

BMI Category	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Data Available	3 (100.0)	82 (98.8)	25 (92.6)
<18.5 (underweight)	1 (33.3)	1 (1.2)	0
18.5-24.9 (normal weight)	0	22 (26.8)	13 (52.0)
25-29.9 (overweight)	1 (33.3)	31 (37.8)	7 (28.0)
>=30 (obese)	1 (33.3)	28 (34.1)	5 (20.0)

[a]BMI = kilograms body weight/(height in meters)^2
N: Number of subjects with pregnancy outcome
% = (n/N) * 100 for the first row; for the other rows, % = n/number of subjects with information available.

Table 9.9. Gravidity at Time of Enrollment

Number of Times Ever Pregnant[a]	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
1	0	32 (38.6)	14 (51.9)
2-3	3 (100.0)	33 (39.8)	10 (37.0)
4-5	0	14 (16.9)	2 (7.4)
>=6	0	4 (4.8)	1 (3.7)

[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 = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
0	2 (66.7)	38 (45.8)	17 (63.0)
1-2	1 (33.3)	43 (51.8)	9 (33.3)
3-4	0	2 (2.4)	0
>=5	0	0	1 (3.7)

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 = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
0	2 (66.7)	54 (65.1)	21 (77.8)
1	1 (33.3)	17 (20.5)	3 (11.1)
2	0	7 (8.4)	2 (7.4)
≥3	0	5 (6.0)	1 (3.7)

[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 = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
0	2 (66.7)	79 (95.2)	26 (96.3)
1	1 (33.3)	4 (4.8)	1 (3.7)
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 = 3)	Diseased Unexposed (N = 83)	Non-Diseased Unexposed (N = 27)
Mean	18.5	20.0	13.4
Standard Deviation	5.9	9.7	4.5
Minimum	11.7	4.6	6.3
1st quartile	16.4	12.0	10.0
Median	21.0	18.3	14.9
3rd quartile	21.9	28.1	17.1
Maximum	22.7	39.0	20.1

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 = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
<13 weeks	1 (33.3)	24 (28.9)	13 (48.1)
13-19.9 weeks	0	20 (24.1)	12 (44.4)
≥20 weeks	2 (66.7)	39 (47.0)	2 (7.4)

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

Table 9.15. Geographic Area of Residence

Country	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
U.S.	3 (100.0)	76 (91.6)	24 (88.9)
Canada	0	7 (8.4)	3 (11.1)

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[a]

	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 = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)
Interfered[a]	0/3 (0.0)	5/83 (6.0)	0/2 (0.0)	3/61 (4.9)	0/1 (0.0)	0/30 (0.0)	0/3 (0.0)	2/46 (4.3)	0/3 (0.0)	3/73 (4.1)
Short of breath[a]	0/3 (0.0)	11/83 (13.3)	0/2 (0.0)	10/61 (16.4)	0/1 (0.0)	3/30 (10.0)	0/3 (0.0)	6/46 (13.0)	1/3 (33.3)	5/73 (6.8)
Up at night[a]	0/3 (0.0)	12/83 (14.5)	0/2 (0.0)	6/61 (9.8)	0/1 (0.0)	2/30 (6.7)	0/3 (0.0)	2/46 (4.3)	0/3 (0.0)	4/73 (5.5)
Rescue med[a]	0/3 (0.0)	12/82 (14.6)	0/2 (0.0)	10/61 (16.4)	0/1 (0.0)	0/30 (0.0)	0/3 (0.0)	3/46 (6.5)	0/3 (0.0)	2/73 (2.7)
Overall rating more severe[a]	0/3 (0.0)	5/83 (6.0)	0/2 (0.0)	6/61 (9.8)	0/1 (0.0)	1/30 (3.3)	0/3 (0.0)	0/46 (0.0)	0/3 (0.0)	2/74 (2.7)
Total score <20 - not well controlled	0/3 (0.0)	32/82 (39.0)	0/2 (0.0)	16/61 (26.2)	0/1 (0.0)	6/30 (20.0)	0/3 (0.0)	10/46 (21.7)	1/3 (33.3)	13/73 (17.8)

[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	
Event	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)
Hospitalized overnight	0/3 (0.0)	0/83 (0.0)	0/1 (0.0)	0/30 (0.0)	0/3 (0.0)	0/47 (0.0)	0/3 (0.0)	0/74 (0.0)
ER visit	0/3 (0.0)	3/83 (3.6)	0/1 (0.0)	0/30 (0.0)	0/3 (0.0)	0/47 (0.0)	0/3 (0.0)	0/74 (0.0)
If yes, Steroid - yes	----	1/3 (33.3)	----	----	----	----	----	----
Unscheduled MD visit	0/3 (0.0)	9/83 (10.8)	0/1 (0.0)	2/30 (6.7)	0/3 (0.0)	2/46 (4.3)	0/3 (0.0)	0/74 (0.0)
If yes, Steroid - yes	----	5/9 (55.6)	----	1/2 (50.0)	----	0/2 (0.0)	----	----
Oral steroid use	0/3 (0.0)	3/83 (3.6)	0/1 (0.0)	1/30 (3.3)	0/3 (0.0)	1/46 (2.2)	0/3 (0.0)	0/74 (0.0)
Any exacerbation (any of the above)	0/3 (0.0)	11/83 (13.3)	0/1 (0.0)	3/30 (10.0)	0/3 (0.0)	3/46 (6.5)	0/3 (0.0)	0/74 (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	
Event	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)
Using medication less than prescribed - yes	0/3 (0.0)	19/83 (22.9)	0/1 (0.0)	7/30 (23.3)	0/3 (0.0)	11/46 (23.9)	1/3 (33.3)	16/74 (21.6)
Quit	----	2/18 (11.1)	----	2/7 (28.6)	----	1/11 (9.1)	0/1 (0.0)	2/15 (13.3)
Reduce	----	16/18 (88.9)	----	5/7 (71.4)	----	10/11 (90.9)	1/1 (100.0)	13/15 (86.7)
Reason[a]								
Pregnancy	----	4/18 (22.2)	----	0/7 (0.0)	----	1/11 (9.1)	0/1 (0.0)	0/16 (0.0)
Feel better	----	8/18 (44.4)	----	4/7 (57.1)	----	8/11 (72.7)	0/1 (0.0)	11/16 (68.8)
Other	----	7/18 (38.9)	----	3/7 (42.9)	----	3/11 (27.3)	1/1 (100.0)	5/16 (31.2)

[a]Subjects may be included more than once as they may have more than one reason for using medication less than prescribed
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 = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Began prior to conception	2 (66.7)	52 (62.7)	16 (59.3)
Post-conception only	1 (33.3)	31 (37.3)	11 (40.7)
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 = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Yes	1 (33.3)	25 (30.1)	13 (48.1)

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 = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Yes	0	3 (3.6)	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 = 3) n(%)	Diseased Unexposed[a] (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Yes	0	3 (3.6)	0

[a]One woman in the Diseased Unexposed group had a fever of 102 for 2 days late in her second trimester, and one woman has a diagnosis of Type II Diabetes, and one woman with exposure to leuprolide acetate post-conception.

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 = 3) n(%)
30 mg every 4 weeks	1 (33.3)
30 mg every 8 weeks	2 (66.7)
Other[a]	0

[a]One shot once per month
N: Number of subjects with pregnancy outcome
% = (n/N) * 100

Table 9.22. Gestational Timing of Benralizumab Use in Pregnancy

Timing of Medication Use in Pregnancy[a]	Benralizumab-Exposed (N = 3) n(%)
Trimester of Medication Use Available	3 (100.0)
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	3 (100.0)
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, of the 2nd trimester is (11, 24] weeks post conception, of 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 both LMP to DOC and the 1st trimester, she will be in the category of 1st Trimester
[b]Last dose occurred in [LMP, DOC)

Table 9.23. GINA Classification during Pregnancy

	Last Menstrual Period (LMP) or First Use of Medication after LMP		32 weeks	
GINA Step Classification[a],[b]	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)	Benralizumab-Exposed (N = 3) n/N'(%)	Diseased Unexposed (N = 83) n/N'(%)
1	0/3 (0.0)	49/83 (59.0)	0/3 (0.0)	25/45 (55.6)
2	0/3 (0.0)	15/83 (18.1)	0/3 (0.0)	7/45 (15.6)
3	0/3 (0.0)	12/83 (14.5)	0/3 (0.0)	10/45 (22.2)
4	0/3 (0.0)	6/83 (7.2)	0/3 (0.0)	3/45 (6.7)
5	3/3 (100.0)	1/83 (1.2)	3/3 (100.0)	0/45 (0.0)
Unable to Classify	0/3 (0.0)	0/83 (0.0)	0/3 (0.0)	0/45 (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 = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Ultrasound Level 1	3 (100.0)	81 (97.6)	26 (96.3)
Ultrasound Level 2	3 (100.0)	72 (86.7)	22 (81.5)
Chorionic villus sampling (CVS)	0	0	0
Amniocentesis	0	2 (2.4)	0

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

Table 9.25. Prenatal Diagnostic Tests Performed prior to Enrollment

	Benralizumab-Exposed (N = 3) n(%)	Diseased Unexposed (N = 83) n(%)	Non-Diseased Unexposed (N = 27) n(%)
Ultrasound Level 1	3 (100.0)	71 (85.5)	21 (77.8)
Ultrasound Level 2	2 (66.7)	38 (45.8)	1 (3.7)
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, 2021 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=3) n/N'(%)	Diseased Unexposed (N=83) n/N'(%)	Non-Diseased Unexposed (N=27) n/N'(%)
Live birth	3/3 (100.0)	74/83 (89.2)	23/27 (85.2)
Twin	0/3 (0.0)	3/74 (4.1)	3/23 (13.0)
Twin with like sex	----	1/3 (33.3)	1/3 (33.3)
Sex (male)	----	1/1 (100.0)	1/1 (100.0)
Twin with non like sex	----	2/3 (66.7)	0/3 (0.0)
Twin with only one surviving	----	0/3 (0.0)	2/3 (66.7)
Sex (male)	----	----	1/2 (50.0)
Singleton	3/3 (100.0)	71/74 (95.9)	20/23 (87.0)
Sex (male)	1/3 (33.3)	35/71 (49.3)	9/20 (45.0)
Cesarean	2/3 (66.7)	25/74 (33.8)	8/23 (34.8)
Spontaneous Abortion[a]	0/3	4/83	1/27
Spontaneous Abortion-Twins	----	0/4	0/1
Stillbirth	0/3 (0.0)	0/83 (0.0)	1/27 (3.7)
Termination	0/3 (0.0)	0/83 (0.0)	1/27 (3.7)
Social	----	----	0
Medical	----	----	1 (100.0)
Lost to Follow Up	0/3 (0.0)	5/83 (6.0)	1/27 (3.7)
No Contact	----	1/5 (20.0)	0/1 (0.0)
Withdrew	----	4/5 (80.0)	1/1 (100.0)

[a]Left Truncation Accounted SAB Rate in Table 10.2
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 Prospectively Enrolled and Exposed prior to 20 Weeks' Gestation and with Follow Up

	Benralizumab-Exposed (N = 1)	Diseased Unexposed (N = 41)	Non-Diseased Unexposed (N = 24)
Number of SAB Events[a]	0	4	1
Left Truncation Accounted SAB Rate[b,c,d,e]	0	36.4%	19.5%

[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]Four LTFU cases were excluded due to having zero days of follow-up: 3 Diseased Unexposed, 1 Non-Diseased Unexposed.
[d]Earliest gestational age at enrollment (weeks): Benralizumab Exposed 11.7, Diseased Unexposed 4.6, Non-Diseased Unexposed 6.3.
[e]Gestational age at Delivery (GAD) was missing for 2 SAB case. Multiple imputation was conducted for cases with missing GAD. The number of imputations was 10.
N: Number of subjects 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	0/3 (0.0)	1/74 (1.4)	1/23 (4.3)
Number of all pregnancies (excluding LTFU) with major birth defects	0/3 (0.0)	1/78 (1.3)	2/26 (7.7)

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	----	0/3 (0.0)	0/3 (0.0)
Number of all pregnancies (excluding LTFU) with major birth defects	----	0/3 (0.0)	0/3 (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

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

	Benralizumab-Exposed n/N(%)	MACDP Reference Rate[a] (%)
Birth Prevalence of major birth defects among all pregnancies excluding LTFU	0/3 (0.0)	---
Birth Prevalence of major birth defects among all pregnancies, excluding LTFU and SAB	0/3 (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. 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)

	Benralizumab-Exposed (N = 3)	Diseased Unexposed (N = 69)	Non-Diseased Unexposed (N = 20)
Number of PTD	1	7	1
Left Truncation Accounted PTD Rate[a],[b]	28.3%	11.0%	4.9%

[a]Computed using Fleming-Harrington estimate at 37 weeks' gestation, accounting for left truncation due to varying time in gestation at enrollment.
[b]Six cases were excluded due to having zero days of follow-up: 5 Diseased Unexposed, 1 Non-Diseased Unexposed.
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 = 3)	Diseased Unexposed (N = 71)	Non-Diseased Unexposed (N = 20)
Mean	38.2	38.7	38.4
Standard Deviation	1.3	2.0	3.5
Minimum	36.9	28.3	24.4
1st quartile	37.6	38.0	37.9
Median	38.4	39.1	39.1
3rd quartile	38.9	40.0	39.9
Maximum	39.4	41.4	41.4

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=3) n/N'(%)	Diseased Unexposed (N=74) n/N'(%)	Non-Diseased Unexposed (N=23) n/N'(%)
Preeclampsia	0/3 (0.0)	6/74 (8.1)	2/23 (8.7)
PIH	0/3 (0.0)	8/74 (10.8)	3/22 (13.6)

% = (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 = 2)	Diseased Unexposed (N = 64)	Non-Diseased Unexposed (N = 19)
Birth Weight - grams	N'= 2	N'= 64	N'= 19
Mean	3260.5	3342.8	3343.6
Standard deviation	239.7	524.5	518.5
Minimum	3091.0	2251.0	2310.0
1st quartile	3175.8	3032.5	3059.2
Median	3260.5	3335.0	3359.0
3rd quartile	3345.2	3584.2	3685.4
Maximum	3430.0	5470.3	4309.1
Birth Length - cm	N'= 2	N'= 63	N'= 17
Mean	49.0	50.7	50.9
Standard deviation	2.8	2.8	1.7
Minimum	47.0	44.5	48.0
1st quartile	48.0	48.3	49.5
Median	49.0	50.8	51.0
3rd quartile	50.0	52.1	52.1
Maximum	51.0	58.4	53.3
Birth Occipitofrontal Circumference - cm	N'= 2	N'= 45	N'= 11
Mean	35.5	34.4	33.7
Standard deviation	0.0	1.7	1.7
Minimum	35.5	30.5	30.5
1st quartile	35.5	33.0	33.2
Median	35.5	34.5	33.5
3rd quartile	35.5	35.6	35.1
Maximum	35.5	37.5	35.6

N: Number of full term singletons.
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=3) n/N'(%)	Diseased Unexposed (N=71) n/N'(%)	Non-Diseased Unexposed (N=20) n/N'(%)
Weight	1/3 (33.3)	11/71 (15.5)	4/20 (20.0)
Length	0/2 (0.0)	3/70 (4.3)	1/18 (5.6)
Occipitofrontal Circumference (OFC)	0/2 (0.0)	11/48 (22.9)	3/11 (27.3)
SGA weight and/or length, but not OFC	0/2 (0.0)	3/67 (4.5)	0/18 (0.0)
SGA weight and/or length, and OFC	0/2 (0.0)	5/67 (7.5)	2/17 (11.8)

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

	Benralizumab-Exposed (N = 2)	Diseased Unexposed (N = 37)	Non-Diseased Unexposed (N = 12)
Weight - percentile	N'= 1	N'= 9	N'= 4
Mean	23.0	23.5	50.2
Standard deviation	----	24.9	30.9
Minimum	23.0	0.1	4.0
1st quartile	23.0	3.0	49.0
Median	23.0	9.0	64.5
3rd quartile	23.0	43.0	65.8
Maximum	23.0	63.0	68.0
Length - percentile	N'= 1	N'= 9	N'= 4
Mean	54.0	45.1	74.8
Standard deviation	----	34.3	17.5
Minimum	54.0	2.0	56.0
1st quartile	54.0	9.0	66.5
Median	54.0	45.0	72.5
3rd quartile	54.0	75.0	80.8
Maximum	54.0	96.0	98.0
Occipitofrontal Circumference - percentile	N'= 1	N'= 9	N'= 4
Mean	74.0	56.4	57.0
Standard deviation	----	32.5	34.5
Minimum	74.0	5.0	26.0
1st quartile	74.0	34.0	28.2
Median	74.0	63.0	54.5
3rd quartile	74.0	77.0	83.2
Maximum	74.0	97.0	93.0

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

	Benralizumab -Exposed (N = 2)	Diseased Unexposed (N = 37)	Non-Diseased Unexposed (N = 12)
Weight <= 10th centile[a]	0/1 (0.0)	5/9 (55.6)	1/4 (25.0)
Length <= 10th centile[a]	0/1 (0.0)	3/9 (33.3)	0/4 (0.0)
Occipitofrontal Circumference <= 10th centile[a]	0/1 (0.0)	1/9 (11.1)	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 10.12. Postnatal Events - Hospitalizations in Infants up to One Year of Age (Including Infants from Multiple Births)

	Benralizumab-Exposed (N=3) n/N'(%)	Diseased Unexposed (N=77) n/N'(%)	Non-Diseased Unexposed (N=24) n/N'(%)
Yes	0/3 (0.0)	5/77 (6.5)	1/24 (4.2)

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

Listing 2. Major Malformations for Diseased Unexposed Group –

Pregnancy ID	Outcome ID	ICD9 Code	Malformation	Mat Age	Race	Multiple Birth	Birth outcome
113825	9381	745.110	Dextro-transposition of the grea arteries (d-TGA) with a Ventricular Septal Defect (VSD)	27.4	White, Non-Hispanic	No	Live birth, 38.7 weeks' gestation

Listing 3. Major Malformations for Non-Diseased Unexposed Group -

Pregnancy ID	Outcome ID	ICD9 Code	Malformation	Mat Age	Race	Multiple Birth	Birth outcome
95981	8271	228.100	Cystic hygroma Diagnosed by fetal ultrasound	36.2	White, Non-Hispanic	No	Termination 13.1 weeks' gestation
96289	8412	1.751.230 2.228.010 3.747.325	1. Imperforate anus with vaginal fistula 2. Sacral Hemangioma: 1.5 x 0.5 cm linear hemangioma on gluteal cleft requiring propranolol[a] 3. Peripheral pulmonic stenosis (PPS)[a]	27.6	Asian, Non-Hispanic	No	Live birth 39.1 weeks' gestation

[a]Not counted per MACDP

11.2. Neonatal or Infant Death anytime by Cohort

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

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

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

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

Listing 7. Hospitalizations – Benralizumab-Exposed Group - None

Listing 8. Hospitalizations – Diseased Unexposed Group -

Pregnancy ID	Outcome ID	Age at Event	Notes
97667	8525	2 months	Hospitalized for 2 weeks due to a positive COVID-19 test. Covid-19 illness lasted for 1 week.
96371	8391	5 days	Hospitalized overnight for neonatal hyperbilirubinemia.
95920	9073	1 month	Hospitalized for febrile and e. coli positive UTI for 3 days. Infection lasted 6 days. Given IV antibiotics in hospital. Continued on oral cephalexin following discharge for a total of 10 days on antibiotics.
105745	9285	1.7 months	Head injury w/ skull fracture. Routine COVID swab was positive but was otherwise asymptomatic. Observation overnight.
113825	9381	3 months.	Admitted for cardiac catheterization with intervention (arterial angioplasty)

Listing 9. Hospitalizations – Non-Diseased Unexposed Group -

Pregnancy ID	Outcome ID	Age at Event	Notes
96289	8412	1.2 months	Hospitalized for 2 days for observation at initiation of propranolol for treatment of the child's hemangioma.

12 PRELIMINARY CONCLUSIONS

The advisory board reviewed the 2021 report and concluded that there are too few data to draw any conclusions and that prevalence of exposure continues to be low. Despite extensive efforts to enhance recruitment (Appendix 1) of the exposed cohort, the investigators concur that the study as currently designed is not feasible to complete in terms of the proposed sample size even if recruitment were extended another five years. The study Sponsor has requested that the regulatory agency consider alternative options to fulfill the post-marketing commitment. While awaiting the final decision on this, the study remains open for recruitment, and subsequent progress and final reports will be delivered as proposed.

Appendix I - Fasenra® Recruitment Summary

Outreach Efforts in Year 3

October 2020 – September 2021

Communication with OTIS Network Members

Throughout the reporting period, study leads had regular communication with the research coordinators at each Teratology Information Service (TIS) site in order to update the coordinators with important information and continue to encourage study referrals. In October 2020, the study team developed a communication toolkit to guide research coordinators at each TIS in talking to potential participants about OTIS/MotherToBaby Pregnancy Studies. In July 2021, the study team sent an email communication to the research coordinators with updates about ongoing studies and encouraged patient referrals.

Digital and Online Advertising

1. Facebook ads specific to asthma and pregnancy, as well as Fasenra® and pregnancy ran during the reporting period. **Paid ads on social media are posts that require payment to distribute to larger or more specific audiences.*
2. Google Display Network advertising was launched in July 2021; these ads target pregnancy study participation based on keywords that a user is searching. **Google Display Network ads are smart ads attached to our study webpage; so if a user searches for the keywords housed on the ongoing study webpage, it will serve the ad in a responsive way based on uploaded assets (images, headlines, logos, videos, and descriptions), and Google will automatically generate ad combinations. For example, a keyword search for "asthma pregnancy Fasenra" or a keyword search for "asthma pregnancy" delivers an ad based on that search that links to our ongoing study webpage and sign-up form. Due to Google advertising restrictions, the ads themselves do not include drug names or indications.*
3. 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.*
4. In October 2020, OTIS launched a new website for MotherToBaby that includes a more modern look and feel with a fresh color palette, an updated design for the PDFs of patient-friendly, bilingual Fact Sheets, and an enhanced user experience for both health professionals and patients. In addition to the update, a new interactive page was created on asthma, which lists information about the study and resources. In addition, healthcare provider pages were created for allergy & immunology, obstetrics, maternal-fetal medicine, family practice, internal medicine, midwifery, and pharmacy; these pages include a list of and links to all related ongoing studies and fact sheets for the field of practice.
5. Information about the study continues to be available on the OTIS/MotherToBaby website, with dedicated study pages for Fasenra® and Asthma. The site accepts both self-referrals from potential participants and healthcare provider-initiated patient referrals.
6. Through February 2021, the OTIS/MotherToBaby's app included information about our ongoing studies and linked the user to a sign-up form during the reporting period. The app was available for both iOS and Android devices and included a clear pathway for health care providers to refer patients. With the launch of the new mobile friendly website in October 2020, the app was retired in March 2021.

7. From January - March 2021, an interactive poll & ad campaign focused on asthma was launched on the WhatToExpect mobile platform. The campaign also included a dedicated e-blast sent to targeted WhatToExpect app users who indicated asthma or asthma treatment during pregnancy. In conjunction with the ads on the WTE platform, OTIS ran retargeting ads on Facebook and Instagram.
8. Study recruitment ads were also displayed in December 2020 and January, February, April, and May 2021 on SMFM's new patient-targeted website, HighRiskPregnancyInfo.org, which launched in late 2020.
9. In April and May 2021, OTIS ran a pilot nationwide programmatic marketing campaign targeting healthcare providers. The ad campaign targeted the following HCP groups to promote OTIS/MotherToBaby Pregnancy Studies and to encourage patient referrals: allergists/immunologists, obstetricians (OBs), maternal-fetal medicine specialists (MFMs), primary care providers, pharmacists, and nurse midwives. Retargeting ads on Facebook were also created and in effect during the campaign.**Programmatic marketing identifies characteristics of target consumers and uses real-time data to purchase bid-based digital ad space in places the audience will see, with ads personalized based on interests and behaviors.*
10. Study recruitment ads were displayed in the October 2020 and January 2021 editions of the *Special Delivery* e-newsletter, which is distributed to the entire membership of the Society for Maternal-Fetal Medicine (SMFM).
11. OTIS/MotherToBaby Pregnancy Studies continue to be listed on ResearchMatch, a free online tool that helps potential research participants find research studies for which they may be eligible.
12. The study is listed on the FDA Pregnancy Registry website under "Asthma" and "Fasenra (benralizumab)."

Outreach to Healthcare Professionals

UC Rely

Referrals continued to be received from UC Rely, a consortium between five University of California Medical Campuses. A coordinator within the Obstetrics Department at each campus screened pregnant women who were potentially eligible for OTIS Studies and, if the woman agreed, she was referred to our coordinating center at UCSD. Each UC Rely site was provided with a patient-oriented FAQs document that could be provided to potential participants at each UC Rely site. In addition, one of the campuses (UCSF) ran digital ads for OTIS Studies in their patient waiting areas.

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. Meetings that occurred within the reporting period were attended virtually due to the COVID-19 pandemic.

MEETING	DATE
American College of Allergy, Asthma & Immunology (ACAAI) – *virtual meeting*	November 2020
Society for Maternal-Fetal Medicine (SMFM) – *virtual meeting*	January 2021
American Academy of Allergy, Asthma & Immunology (AAAAI)** – *virtual meeting*	February 2021
American Pharmacists Association (APhA) – *virtual meeting*	March 2021

Academy of Managed Care Pharmacy (AMCP) – *virtual meeting*	April 2021
American College of Obstetricians and Gynecologists (ACOG) – *virtual meeting*	April 2021
American Thoracic Society – *virtual meeting*	May 2021
American College of Nurse-Midwives (ACNM) – *virtual meeting*	May 2021
American Association of Physicians Assistants – *virtual meeting*	May 2021
American Academy of Family Physicians (AAFP) – *virtual meeting*	July 2021

**For the AAAAI meeting, the study team developed a postcard that AAAAI distributed to their membership and to conference attendees that highlighted OTIS/MotherToBaby's resources, ongoing studies, and virtual exhibit booth information.

Post-Conference Email Marketing

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 (see below).

OTIS E-Newsletter

OTIS maintains a listserv of healthcare professionals and pushes out periodic e-newsletters. The content highlights the studies, encourages referrals, and announces new relevant resources and materials that are available to order. Newsletter content is curated to different health professional specialty groups. An e-newsletter was sent to pregnancy-related healthcare providers (including OBs, MFMs, family practice, and nurse midwives) in November 2020 and June 2021 and to allergists/immunologists in July 2021.

SMFM *Special Delivery* E-Newsletter

SMFM continued to include a list of newly added/updated OTIS/MotherToBaby fact sheets in their monthly e-newsletter, as well as a pregnancy registry spotlight that promoted ongoing studies. In August 2021, the pregnancy registry spotlight was on OTIS' asthma medications studies.

Other Presentations and Outreach Efforts:

National Birth Defects Prevention – #Best4YouBest4Baby Twitter Chat

In January 2021, OTIS/MotherToBaby participated in a month long awareness campaign which included co-hosting a bi-lingual twitter chat focused on preventable causes of birth defects to coincide with National Birth Defects Prevention Month. During the chat, specific promotional tweets of OTIS/MotherToBaby pregnancy studies were posted. Some partner organizations who participated included March of Dimes and the CDC's National Center on Birth Defects and Developmental Disabilities (NCBDDD).

World Birth Defect Day - Live Q & A

In March 2021, MotherToBaby hosted a live panel Q & A to coincide with World Birth Defect Day, The panel discussion was streamed on Facebook and featured Dr. Christina Chambers, Dr. Kenneth Lyons Jones, and Dr. Miguel Del Campo. The discussion included promotion of the study and encouraged referrals and enrollments.

National Public Health Week Live Twitter Chat

In April 2021, OTIS participated in the NPHW live twitter chat and promoted OTIS/MotherToBaby Studies and resources.

Black Maternal Health Week

From April 11-17, 2021, OTIS participated in BMWH online activities and promoted OTIS/MotherToBaby Studies and resources.

MotherToBaby: April Featured Blog

In April 2021, OTIS published an educational article on pregnancy registries, promoting the study and encouraging enrollments. Additional promotional activities took place in tandem with the blog publication, including social media posts, partner sharing and paid advertising.

HRSA Women's Health Live Twitter Chat

On May 12, 2021, OTIS participated in a live twitter chat hosted by HRSA on women's health, and promoted OTIS/MotherToBaby Studies and resources.

Strategic Partnerships

Allergy & Asthma Network

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

Society of Maternal-Fetal Medicine (SMFM)

As noted above, SMFM includes lists of newly added/updated OTIS/MotherToBaby fact sheets in their monthly e-newsletter, as well as a pregnancy registry spotlight which promotes the study. Additional partnership activities also took place for January 2021 in recognition of National Birth Defects Prevention Month (e.g., blog sharing, social media sharing/promo, joint participation in Twitter chat with March of Dimes).

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.

MyHealthTeams – My Asthma Team

OTIS continued to send quarterly updates of any new and relevant materials for promotion on patient/member forums.

TheMighty

MotherToBaby maintains a partner profile page on this organization's site directing their members who indicate an interest regarding asthma 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

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

The "Benralizumab (Fasenra®) in Pregnancy" and the "Asthma in Pregnancy" Fact Sheets continue to be 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 were available for free download in both English and Spanish and were mailed and/or emailed to health care providers as part of outreach efforts.

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 November 2020 and March 2021 issue of Practice Matters, a bi-weekly newsletter to AAAAI members which included information on the VAMPSS study.
- In May 2021, a dedicated email was sent to all AAAAI members encouraging provides to refer patients to the study as part of Allergy and Asthma Awareness Month.
- On AAAAI's COVID-19 Resources page, Dr. Jennifer Namazy authored an article on "Caring for your pregnant patients with asthma" and provides updates monthly.
- During the AAAAI Virtual Annual Meeting, our AAAAI partners:
    - Featured the study in the Practice Management Hub
    - Included a COVID-19 vaccine survey for allergists related to their pregnant patients and patients on biologic therapies
    - Promoted the study at a live workshop on Asthma Biologics During Pregnancy: Safety and Use (also recorded)

Sponsor Activities

US & Canadian Active Prescriber Communications

In February 2021, OTIS drafted a communication promoting the study which the sponsor distributed to Fasenra® top prescribers. The communication included information on the study and how to refer patients.

Patient Order Form

In October 2020, approval was received to add a checkbox for referral to the study on the AZ Fasenra patient order form.

Appendix II - Literature Review

Successful pregnancy in the setting of eosinophil depletion by benralizumab

Scott Manetz, PhD[a], Irina Maric, MD[b], Thomas Brown, RN[c], Fei Li Kuang, MD, PhD[d], Lauren Wetzler, MHS, PA-C[c], Elizabeth Battisto, DO[e], and Amy D. Klion, MD[c]

Clinical Implications

- Eosinophil-depleting therapies have shown benefit in women of childbearing age. Although the risks and benefits of these agents in pregnant women with hypereosinophilia have not been established, this study demonstrates that eosinophils are not required for normal human development.

With widespread availability of mAbs for the treatment of eosinophilic disorders affecting women of childbearing age, safety during pregnancy has become an important issue. Although the package inserts for mepolizumab, reslizumab, and benralizumab indicate insufficient safety data in pregnancy, these drugs have demonstrated great benefit in the treatment of severe asthma and are likely to be prescribed to women of childbearing age. We describe a patient with hypereosinophilic syndrome who became pregnant while receiving benralizumab on a clinical trial and delivered a healthy baby without eosinophils. Nonhuman primate data supporting the safety of benralizumab during pregnancy are also provided.

The mother is a 36-year-old woman with hypereosinophilic syndrome and severe eosinophilic gastrointestinal involvement (see Kuang et al[1] for her clinical history and benralizumab response before becoming pregnant [patient 16]). She was unexpectedly found to be pregnant at a routine benralizumab administration visit (week 128; NCT02130882). After discussion with the National Institutes of Health Institutional Review Board, the National Institutes of Health Investigational New Drug sponsor, and AstraZeneca, she was allowed to continue benralizumab therapy. At 38 weeks of gestation (July 18, 2019), she delivered a 3091-g healthy baby girl by primary cesarean section for failure to progress. APGAR scores were 8 and 9 at 1 and 5 minutes, respectively. Physical examination of the neonate was entirely normal. Complete blood cell count at birth showed a white blood cell count of 22,500/μL with 0 eosinophils/μL. State-mandated newborn screening revealed a mildly elevated thyroid-stimulating hormone level (with normal free T4 level) that decreased over the ensuing months. The patient elected not to breast-feed. The baby's growth and development have been within normal limits. She has been healthy (no sick visits) without eczema, food allergy, or other evidence of atopic disease. Her absolute eosinophil count remained undetectable until age 7 months at which time it was 228/μL (normal range for age, 700-1000/μL; Figure 1). Repeat absolute eosinophil count at age 1 year was 258/μL. Platelets began to rise at age 1 month, peaking at age 7 months at 723 k/μL before returning to near-normal values (492 k/μL) at 1 year. The remainder of her complete blood cell count has been consistently within normal limits (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Peripheral blood smear review and flow cytometric staining of whole blood at age 1 year confirmed the presence of phenotypically normal eosinophils. She received pneumococcal conjugate vaccine at 4, 6, 9, and 12 months. Protective pneumococcal antibody levels to 12 of 12 tested serotypes included in the pneumococcal conjugate vaccine 13 and 0 of 11 tested serotypes not included in the vaccine were demonstrated at 12 months (see Table E2 in this article's Online Repository at www.jaci-inpractice.org), consistent with an appropriate vaccine response.

A Good Laboratory Practice–compliant enhanced prenatal and postnatal development study was performed in cynomolgus monkeys. Pregnant monkeys received benralizumab 10 mg/kg (n = 14), 30 mg/kg (n = 21), or control (n = 15) every 14 days beginning at day 20 to 22 of gestation through delivery (for additional details, see this article's Online Repository text at www.jaci-inpractice.org). Growth and development were normal throughout gestation and postnatal follow-up (6.5 months) in the monkeys exposed to benralizumab *in utero*. The only benralizumab-related effect was depletion of eosinophils, which resolved by 180 days of life in all but 1 infant monkey (in the 30 mg/kg exposure group) (Figure 2). No abnormalities were observed in other leukocyte subsets, hemoglobin levels, or platelets counts. Benralizumab administration resulted in depletion of bone marrow eosinophils in the same infant monkey that lacked detectable peripheral blood eosinophils. No other bone marrow changes were observed. Serum levels of IgG, IgM, and IgA and the T-cell–dependent antibody response to primary keyhole limpet hemocyanin immunization were within normal limits and comparable to control animals. Serum half-life of repeated dose intravenous benralizumab (10-30 mg/kg) in adult cynomolgus monkeys is 11 to 17 days (compared with ~15 days in adult humans[2]).

Although murine models have demonstrated no evidence of teratogenicity or reproductive toxicity in the absence of eosinophils, eosinophil-less mice have been shown to have subtle abnormalities of homeostatic function, including impaired recall responses to vaccines.[3] These findings raise theoretical concerns for babies born to mothers receiving eosinophil-depleting antibodies that cross the placenta, including benralizumab. Since Food and Drug Administration approval for use in severe asthma in adults and children 12 years or older in November 2017, more than 8000 individuals have received benralizumab in clinical trials. To date, there have been no reports of unexpected toxicities, and a large study examining antibody responses to seasonal influenza vaccination showed no impairment of responses in patients with asthma receiving benralizumab.[4] The only published report of benralizumab in human pregnancy to date is an abstract describing a woman with marked eosinophilia (6940/μL), asthma, multifocal pulmonary infiltrates, and eosinophilic pericarditis, well controlled on benralizumab, who relapsed with drug discontinuation.[5] Benralizumab was restarted at 20 weeks of gestation and continued through parturition. No further information is provided.