TERIFLUNOMIDE PREGNANCY OUTCOME EXPOSURE REGISTRY: AN AUTOIMMUNE DISEASES IN PREGNANCY PROJECT

STUDY NUMBER: OBS13499

2023 Addendum I to the Final 2023 Annual Interim Report
Covering Updates Between 21 June 2023 to 16 December 2023

09 April 2024

Contents

Abbreviations

DOC	Date of Conception
EDC	Estimated Date of Confinement / Estimated Due Date
LMP	Last Menstrual Period
LTFU	Lost-to Follow-up
MS	Multiple Sclerosis
OTIS	Organization of Teratology Information Specialists
SAB	Spontaneous Abortion
US	United States
US-FDA	United States – Food and Drug Administration

1 PURPOSE AND RATIONALE FOR THE REGISTRY

The purpose of the Teriflunomide Pregnancy Outcome Exposure Registry: An OTIS Autoimmune Diseases in Pregnancy Project was to monitor pregnancies in women with multiple sclerosis (MS) exposed to teriflunomide, in order to evaluate the possible teratogenic effects of this medication on the pregnancy outcome. The lack of sufficient human fetal safety data for teriflunomide makes such a monitoring system an important component of epidemiologic research on the safety of this drug. In addition, the purpose of the registry study was to serve as an educational resource for clinicians who prescribe teriflunomide and for women of reproductive age who are taking teriflunomide.

2 STUDY OBJECTIVES

The objectives of this cohort pregnancy registry was to 1) estimate the risk of birth defects and other adverse pregnancy outcomes occurring in offspring of women exposed to teriflunomide during pregnancy and 2) to detect any increase in the prevalence or pattern of these outcomes among exposed pregnancies. Determination of risk in the teriflunomide exposed group was planned to be based on a primary comparison to a disease-matched group and a secondary comparison to a non-disease control group. Structural defects were classified according to external data from a population-based birth defects surveillance program (The Metropolitan Atlanta Congenital Defects Program [MACDP]).

3 RESULTS

The Teriflunomide Pregnancy Outcome Exposure Registry was established in April 2013, and the first subject was recruited April 15, 2013. The overall recruitment goals for the cohort study were set at 75 in the teriflunomide-exposed cohort, and 125 participants in each of the 2 comparison cohort groups, (325 subjects in total). Due to low recruitment into the teriflunomide-exposed cohort, the study was closed to enrollment on April 3, 2023. Follow-up was discontinued in the comparison groups as of December 16, 2023, while follow-up of participants enrolled into the teriflunomide-exposed cohort and teriflunomide case-series group will continue until the children of those participants reach 1-year of age.

Between April 15, 2013, and April 3, 2023 (end of enrollment), 220 participants were enrolled: 212 into the cohort study, and 8 into the teriflunomide case-series. Of those enrolled, 12 participants were enrolled into the teriflunomide-exposed cohort group, and 8 participants in the teriflunomide-exposed case-series, 111 were enrolled into the disease unexposed group, and 89 participants in the non-diseased unexposed group. No additional participants were enrolled since the data-cut for the 2023 annual interim report on June 21, 2023 (Table 1).

Table 1. Recruitment and Referral Source for All Enrolled Subjects and Teriflunomide-Exposed Declined

	Teriflunomide Exposed (Cohort I)	Teriflunomide Exposed Registry[a]	Diseased-Unexposed (Cohort II)	Non-Diseased Unexposed (Cohort III)
Recruitment Goal	75	--	125	125
Enrolled Subjects	12	8	111	89
Referral Source				
Sponsor	5	2	0	1
Health-care Professional	5	4	15	8
UC Rely[b]	0	0	1	4
Internet	1	2	78	56
Patient Support Group	0	0	7	1
OTIS Member Service	0	0	5	16
Other[c]	1	0	5	3

[a]Subjects were exposed to teriflunomide during pregnancy but did not meet the prospective cohort eligibility criteria. Descriptive tables for these subjects follow the descriptive tables for the cohort
[b]UC Rely is a consortium of obstetric groups at 4 of the University of California (UC) medical centers.
[c]Includes, but is not limited to, repeat caller, referral by a friend, and the medication label

As of the data-cut on December 16, 2023, pregnancy outcomes have been collected on 215 pregnancies: of which 183 outcomes were live born infants, 9 pregnancies resulted in spontaneous abortions, 1 pregnancy ended in a stillbirth, and 22 pregnancies were deemed lost-to follow-up (17 no contact, and 5 participants withdrew) (Table 2). This includes the following updates since the data presented in the 2023 annual interim report (June 21, 2023 data-cut): 1 lost-to follow-up (no contact) in the teriflunomide-exposed cohort, 1 live birth and 1 lost-to follow-up (no contact) in the Disease Unexposed cohort, and 3 live births, and 2 pregnancies that were lost-to follow-up (1 no contact, 1 withdrawal) in the non-disease unexposed cohort. Five pregnancies are pending outcome, 2 in the diseased unexposed cohort and 3 in the unexposed cohort, as of the data-cut on December 16, 2023.

Table 2. Pregnancy Outcomes

	Teriflunomide Exposed (Cohort I) (N = 12) n/N' (%)	Teriflunomide Exposed Registry (N = 8) n/N' (%)	Diseased-Unexposed (Cohort II) (N = 111) n/N' (%)	Non-Diseased Unexposed (Cohort III) (N = 89) n/N' (%)
Known Pregnancy Outcome	12./12 (100.0)	8/8 (100.0)	109/111 (98.2)	86/89 (96.6)
Live born	6/12 (50.0)	6/8 (75.0)	94/111 (84.7)	77/89 (86.5)
SAB[1]	2/12 (16.7)	1/8 (12.5)	1/111 (0.9)	5/89 (5.6)
Stillbirth	0/12 (0.0)	0/8 (0.0)	1/111 (0.9)	0/89 (0.0)
TAB[2]	0/12 (0.0)	0/8 (0.0)	0/111 (0.0)	0/89 (0.0)
LTFU [3] Outcome	4/12 (33.3)	1/8 (12.5)	13/109 (11.9)	4/86 (4.7)
No Contact	3/4 (75.0)	1/1 (100.0)	11/13 (84.6)	2/4 (50.0)
Withdrew	1/4 (25.0)	0/1 (0.0)	2/13 (15.4)	2/4 (50.0)
Pending Outcome:	0/12 (0.0)	0/8 (0.0)	2/111 (1.8)	3/89 (3.4)
Total:	12./12 (100.0)	8/8 (100.0)	111/111 (100.0)	89/89 (100.0)

1. Spontaneous abortion (SAB)
2. Termination of pregnancy (TAB)
3. Lost-to Follow-up (LTFU))

Seventeen pregnancies ended with a major malformation, 1 in the teriflunomide-exposed cohort (post-axial polydactyly, Type B), 12 in the diseased unexposed cohort, and 4 in the non-diseased unexposed cohort (Table 4). No pregnancies with major malformations were identified between the 2023 annual interim report (data-cut June 21, 2023) and this report (data-cut December 16, 2023). No neonatal deaths have been reported in the teriflunomide-exposed cohort.

Table 4. Major Birth Defects

	Teriflunomide-Exposed (Cohort I) n/N(%)	Teriflunomide-Exposed Registry n/N(%)	Diseased Unexposed (Cohort II) n/N(%)	Non-Diseased Unexposed (Cohort III) n/N(%)
Number of pregnancies ending with at least one live born infant with a major birth defect	1/6 (16.7)	0/6 (0.0)	12/94 (12.8)	4/77 (5.2)
Number of all pregnancies (excluding LTFU) with major birth defects	1/8 (12.5)	0/7 (0.0)	12/96 (12.5)	4/82 (4.9)

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

4 CONCLUSION

The Teriflunomide Pregnancy Exposure Registry: An Autoimmune Diseases in Pregnancy Project (study number: OBS13499) was terminated, after 10 years of recruitment, at the request of the Sponsor due to low enrollment in the teriflunomide-exposed cohort. Between April 15, 2013 and December 16, 2023, 12 participants were enrolled in the teriflunomide-exposed cohort, and 8 participants were enrolled in the teriflunomide-exposed case-series. One major malformation (post-axial polydactyly, Type B) was reported in the teriflunomide-exposed cohort, and no major malformations were reported in the teriflunomide exposed case-series.

The limited sample size recruited for this study does not support drawing conclusions about the safety of teriflunomide in pregnancy. However, the one major malformation reported among the teriflunomide-exposed pregnancies is consistent with the expected numbers of major malformations in the general population