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Pregnancy Outcomes in Partners of Male Study Participants Treated With Teriflunomide

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INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing–remitting MS
- Exposure to teriflunomide exceeds 6800 patient-years across more than 12 years of the clinical program
- Teriflunomide is the principal active metabolite of leflunomide, approved for treatment of rheumatoid arthritis (RA) since 1998[1]
  - Embryo lethality and teratogenicity were observed in teriflunomide[1] and leflunomide[2] animal studies
  - In the prospective Organization of Teratology Information Specialists (OTIS) registry, patients with RA who were exposed to leflunomide in their first trimester of pregnancy underwent an accelerated elimination procedure[3]
  - No significant differences were demonstrated in the overall rate of major structural defects in babies born to women treated with leflunomide compared with those born to disease-matched and healthy controls. There was no evidence of teratogenicity, and the rate of spontaneous abortion was similar to that expected in the general population[3]
  - There has been no teratogenicity signal for leflunomide in post-marketing surveillance with over 2.3 million patient-years of exposure
  - Data on pregnancies in the teriflunomide clinical trial program have not shown a teratogenic signal
- The risk of male-mediated embryo-fetal toxicity with teriflunomide is considered low[1]
  - In humans, the estimated female exposure via semen of a treated patient is expected to be 100 times lower than the steady state plasma exposure with teriflunomide 14-mg oral dosing

OBJECTIVE

- To report pregnancy outcomes in partners of male study participants in the teriflunomide clinical program
- To examine existing preclinical data to determine whether teriflunomide could potentially affect male reproduction

METHODS

Preclinical Studies

- The following genotoxicity tests were performed:
  - In vitro: Ames, hypoxanthine-guanine phosphoribosyltransferase (HPRT), and chromosome aberration tests[4–6]
  - In vivo: micronucleus and chromosome aberration tests[7,8]
  - The effect of addition of uridine on results for teriflunomide in the in vitro chromosome aberration test was also measured
- Tissue distribution was assessed using quantitative whole-body autoradiography following a single oral dose of ^{14}C-teriflunomide 7.5 mg/kg to adult rats. Testes and epididymis radioactivity concentrations were determined by liquid scintillation counting. Sprague Dawley (SD; albino) rats were used for time points up to 72 hours, and Long Evans (LE; pigmented) rats were used for follow-up to 28 days
- The effects of teriflunomide on the male reproductive performance and fertility were evaluated following oral administration of teriflunomide 1, 3, or 10 mg/kg/day (10 mg/kg/day is the maximally tolerated dose) to male rats for more than one spermatogenesis cycle (>70 days) before breeding with untreated female rats. Sperm count and motility were evaluated. Mating and pregnancy indices were calculated. The fetuses of untreated females bred to the treated males were examined externally on gestation Day 21

Pregnancies

- In the clinical development program, patients received teriflunomide (14 mg or 7 mg), interferon beta (IFNβ), placebo, or a combination of treatments (**Figure 1**)
- This presentation includes information on pregnancies in partners of male patients and their outcomes collected through October 18, 2013

RESULTS

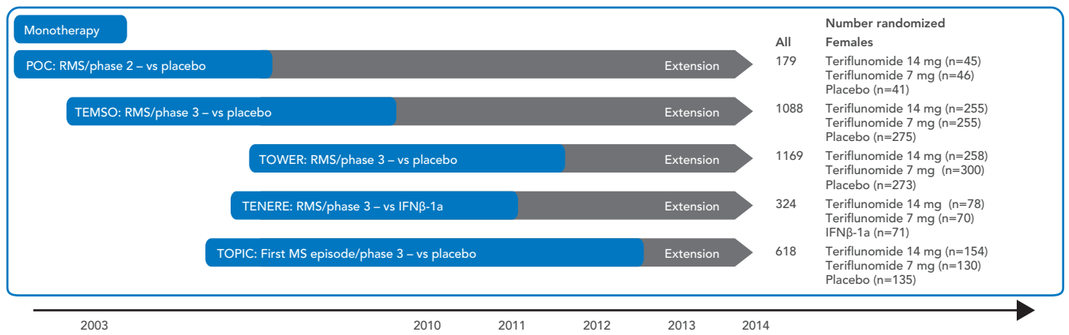
Genotoxicity Assessment

- Teriflunomide was nonmutagenic in vitro in either the Ames test or the HPRT test and was not clastogenic in the in vivo micronucleus and chromosome aberration tests in three species (mouse, rat, and Chinese hamster)
- In the in vitro chromosome aberration test in human lymphocytes, the result for teriflunomide was negative at clinical exposures (45.3 µg/mL [mean predicted human teriflunomide steady state maximum concentration (C_{max}) at the 14-mg dose])
  - However, at concentrations ≥6-fold higher (≥300 µg/mL), the result was positive. This result was attributed to an indirect effect on DNA synthesis caused by the nucleotide pool imbalance in vitro due to the inhibition of DHODH and consequent impairment of pyrimidine biosynthesis in the static in vitro system
  - When the in vitro chromosome aberration test was conducted with the addition of 500 µM uridine, the effects of teriflunomide on mitotic index were reduced, as were the number of cells with chromosome aberrations

Tissue Distribution

- Concentrations of radioactivity in adult rats administered ^{14}C-teriflunomide were lower in the testes and epididymis than in blood (**Figure 2**)
  - Radioactivity concentrations in epididymis and testes were 22%–46% of those in blood at 6 hours post dose. By Day 14, levels were below the limit of quantification in both epididymis and testes (**Figure 2B**). Because the spermatogenesis cycle is longer than 14 days (56 days), this suggests that teriflunomide does not bind irreversibly to sperm

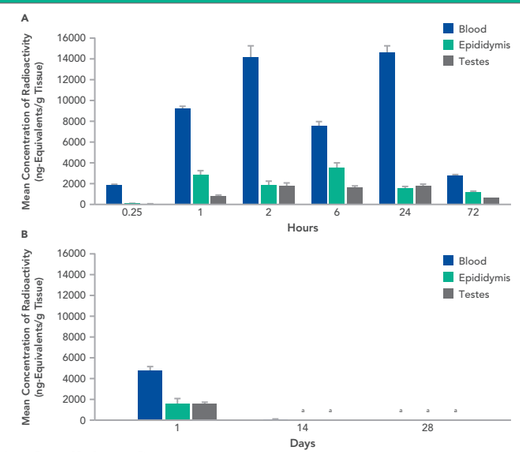
Figure 1. Teriflunomide Clinical Development Plan



	All	Number randomized Females
POC: RMS/phase 2 – vs placebo	179	Teriflunomide 14 mg (n=45) Teriflunomide 7 mg (n=46) Placebo (n=41)
TEMSO: RMS/phase 3 – vs placebo	1088	Teriflunomide 14 mg (n=255) Teriflunomide 7 mg (n=255) Placebo (n=275)
TOWER: RMS/phase 3 – vs placebo	1169	Teriflunomide 14 mg (n=258) Teriflunomide 7 mg (n=300) Placebo (n=273)
TENERE: RMS/phase 3 – vs IFNβ-1a	324	Teriflunomide 14 mg (n=78) Teriflunomide 7 mg (n=70) IFNβ-1a (n=71)
TOPIC: First MS episode/phase 3 – vs placebo	618	Teriflunomide 14 mg (n=154) Teriflunomide 7 mg (n=130) Placebo (n=135)

GA, glatiramer acetate; IFNβ, interferon beta; POC, proof of concept; RMS, relapsing MS.
Phase 2 POC, NCT01487096; Phase 2 monotherapy extension, NCT00228163; TEMSO core study, NCT00134563; TEMSO extension, NCT00803049; TOWER, NCT00751881; TENERE, NCT00883337; TOPIC, NCT00622700; Phase 2 IFNβ adjunctive study, NCT00489489; Phase 2 GA adjunctive study, NCT00475865; Phase 2 IFNβ and GA adjunctive extension, NCT00811395.
The clinical development program included three adjunctive therapy studies. The phase 2 IFNβ adjunctive study randomized 118 patients (females: IFNβ + teriflunomide 14 mg, n=27; IFNβ + teriflunomide 7 mg, n=24; IFNβ + placebo, n=31). The phase 2 GA adjunctive study randomized 123 patients (females: GA + teriflunomide 14 mg, n=32; GA + teriflunomide 7 mg, n=33; GA + placebo, n=32). The phase 3 TERACLES study (NCT0122355) randomized 534 patients (females: IFNβ + teriflunomide 14 mg, n=114; IFNβ + teriflunomide 7 mg, n=125; IFNβ + placebo, n=113).

Figure 2. Concentrations of Radioactivity in Tissues of (A) SD Rats and (B) LE Rats Dosed With ^{14}C-teriflunomide

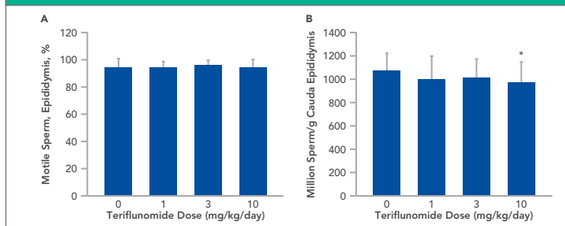


LE, Long Evans; SD, Sprague Dawley.
n=4/Tissue; error bars show standard deviations of readings; [a]radioactivity level could not be distinguished from background.

Effects on Male Fertility

- Teriflunomide treatment of male rats had no effect on sperm motility at any dose tested, and had only a small effect (12% reduction) in sperm count at the highest dose tested (10 mg/kg/day) (**Figure 3**)

Figure 3. Sperm Motility (A) and Count (B) in Teriflunomide-Treated Male Rats



n=25–26 rats per dose; error bars show standard deviation; *P<0.05 compared with untreated rats.

- Furthermore, teriflunomide treatment had no effect on male fertility or reproductive performance[9]
- There were no external malformations in the offspring of male rats treated with teriflunomide before mating with untreated female rats[9]

Pregnancies in Partners of Male Patients

- Twenty-two pregnancies were reported in partners of male patients enrolled into teriflunomide clinical trials (**Table 1**)
- In 19 pregnancies, the father had been treated with teriflunomide; in three pregnancies, the father had received placebo
- There were 18 live births, 16 to partners of male patients who had been exposed to teriflunomide
  - All newborns were healthy and free from structural and functional abnormalities at birth
- Two induced abortions and one spontaneous abortion were reported in the teriflunomide group; one induced abortion was reported in the placebo group
  - No induced abortions were performed because of defects or malformations

Table 1. Number of Pregnancy Outcomes in Partners of Male Patients

	Teriflunomide	Placebo
Live birth	16	2
Induced abortion	2	1
Spontaneous abortion	1	0
Total	19	3

CONCLUSIONS

- All newborns born to partners of male patients treated with teriflunomide had no structural or functional abnormalities at birth
  - These findings are consistent with a lack of teratogenicity for leflunomide overall, with findings in female patients treated with teriflunomide in the teriflunomide clinical trial program, etc., and with pregnancy outcomes from the OTIS registry reported for female patients with RA treated with leflunomide
- Results of in vitro and in vivo studies in animals did not indicate a signal for genotoxicity at the clinical exposure levels of teriflunomide
- In rats, teriflunomide exposure in the testes and epididymis was lower than in the blood. Though a small effect on sperm count was observed at the highest teriflunomide dose, there was no effect on fertility or reproductive performance. The fetuses of teriflunomide-treated male rats showed no external malformations
- Teriflunomide is a therapeutic option for women of childbearing potential and for male patients with female partners of childbearing potential when using effective contraception

The OTIS pregnancy registry is collecting prospective data from pregnancies in the post-marketing setting: www.pregnancystudies.org; tel: 1-877-311-8972

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