Teriflunomide is the principal active metabolite of leflunomide, approved for treatment of rheumatoid arthritis (RA) since 1998. 

- Exposure to teriflunomide exceeds 6800 patient-years across more than 12 years of clinical program

Teriflunomide is an oral pyrimidine synthetase inhibitor. It is known to be a potent immunosuppressant, with demonstrated efficacy in multiple sclerosis (MS) trials. 

- The clinical development program included three adjunctive therapy studies. The phase 2 IFN β-1a phase 2/3 extension study randomized 118 patients (females: IFN β-1a placebo, n=70; teriflunomide 7 mg, n=30) to placebo or teriflunomide 7 mg.

RESULTS

Genotoxicity Assessment

Teriflunomide was nonmutagenic in vitro in 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). The results of the in vitro chromosome aberration test in human lymphocytes, the result for teriflunomide was negative at all clinical exposures (4.5 μM; mean predicted human female steady state maximum concentration: Cmax at the 14-mg dose).

Effects on Male Fertility

- Teriflunomide treatment of male rats had no effect on sperm motility at any dose treated, and no effect on sperm count was observed at the highest dose tested (10 mg/kg/day).

- Furthermore, teriflunomide treatment had no effect on male fertility or reproductive performance.

- There were no external malformations in the offspring of male rats treated with teriflunomide.

Pregnancies in Partners of Male Patients

- Twenty-two pregnancies were reported in partners of male patients enrolled into the 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.

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, 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 treatment in the testes and epididymis was lower in the blood. Though a small effect on sperm count was observed at the highest dose tested, there was no effect on fertility or reproductive performance.

- The 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 registry is collecting prospective data from pregnancies in the Phase 2 and 3 programs. For more information, please visit www.otisregistry.org.

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

<table>
<thead>
<tr>
<th>Number of Pregnancy Outcomes</th>
<th>Male Patients</th>
<th>Female Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Induced abortion</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

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