Teriflunomide International Pregnancy Registry: Enrolment Update

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OBJECTIVE

- **To report the study design and enrolment results for the International Teriflunomide Pregnancy Exposure Registry**

CONCLUSIONS

- **The International Teriflunomide Pregnancy Exposure Registry will provide outcomes on teriflunomide-exposed pregnancies, as well as infant development during the first year of life**
- **Findings from this registry, together with those of the US/Canadian Teriflunomide Pregnancy Exposure Registry, will inform HCPs when counselling women exposed to teriflunomide during pregnancy**

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INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of patients with relapsing forms of MS in more than 80 countries, with 285,000 patient-years of real-world exposure as of March 2019
- In addition to a consistent, well-characterised safety and tolerability profile, teriflunomide has demonstrated consistent efficacy on clinical and MRI disease activity in patients with RRMS and in those who experienced a first clinical episode suggestive of MS[1-4]
- Use of teriflunomide is contraindicated in pregnant women and in women of reproductive potential who are not using effective contraception because of the potential for foetal harm and the observation of teratogenicity and embryo lethality in the offspring of teriflunomide-treated rats and rabbits[5]
- Teriflunomide elimination can be accelerated in patients by the administration of cholestyramine or activated charcoal after stopping teriflunomide treatment[5]
- Teriflunomide is the principal active metabolite of leflunomide (approved since 1998 for the treatment of rheumatoid arthritis)[6]
  - Studies conducted by the Organization of Teratology Information Specialists found no significant differences in rates of major structural defects and no pattern of minor or major anomalies in newborns of women exposed to leflunomide compared with disease-matched or healthy comparator groups[7,8]
- Data from pregnancies that occurred during teriflunomide exposure do not suggest an increased risk of adverse outcomes, nevertheless it is important to collect data from teriflunomide-exposed pregnancies to evaluate any potential adverse outcomes[9]
- Global teriflunomide pregnancy registries have been established to capture prospective data from pregnancies within the postmarketing setting

METHODS

Registry Design

- This is an ongoing, voluntary, multinational, prospective, observational, exposure-registration study conducted in Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, and the UK (**Figure 1**)
- The registry design and inclusion/exclusion criteria are shown in **Figure 2** and **Table 1**, respectively
- National Coordinators liaise with health care professionals (HCPs) to collect information on teriflunomide-exposed pregnancies and oversee enrolment in the registry
- To enrol a patient, HCPs can contact the National Coordinating Centre in their country
  - **For UK contact: Manchester Centre for Clinical Neurosciences; 0161 206 0534; neuroresearch.nurse@srft.nhs.uk**

Outcomes

- **Table 2** outlines the primary and secondary objectives of the registry
- Pregnancy outcomes and infant characteristics during the first year of life are being collected (**Table 3**)

Statistical Analysis

- The registry aims to enrol 196 pregnant women, projected to result in 104 live births; this sample size is estimated to provide an 80% power to detect a 3.95-fold increase in risk ratio of birth defects associated with teriflunomide exposure versus EUROCAT[10]
- Analyses will be based on prospective cases of women with teriflunomide exposure during pregnancy prior to the knowledge of pregnancy outcome and will be conducted in 3 populations
  - **Primary analysis population:** Eligible pregnant women with available pregnancy outcomes and birth defect status of any infant(s) available at birth or 1-year follow-up. Used for evaluation of primary objective and rate of birth defects (secondary objective)
  - **Pregnant woman population:** Eligible pregnant women with pregnancy outcomes available. Used for evaluation of secondary objectives related to pregnancy outcomes
  - **Live infant population:** All live-born infants from the pregnant woman population. Used for evaluation of secondary objectives related to live births
- Retrospective cases are not included in the calculation of birth defect rates (but will be summarised separately in interim and final reports)
- Teriflunomide pregnancy exposure data will be classified by gestational week and trimester

Figure 1. Map of Countries Participating in the International Teriflunomide Pregnancy Exposure Registry

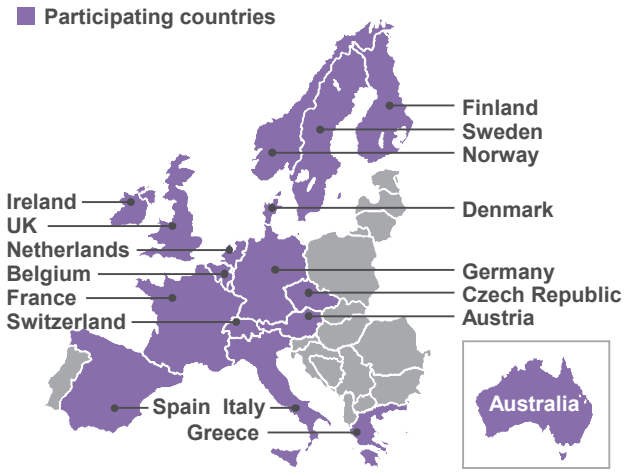

Figure 2. Registry Design[11]

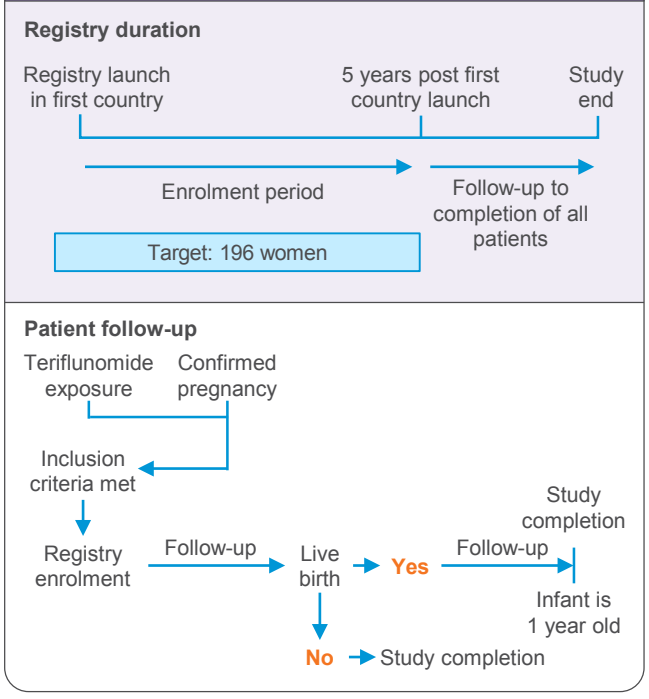

Table 1. Inclusion and Exclusion Criteria[11,a]

Inclusion criteria	**Pregnant women with MS who:** • Have teriflunomide exposure (any dose, any duration, any time) after Day 1 of last menstrual period until pregnancy end • Receive health care in the participating countries • Provide written informed consent • Authorise release of medical information for self and live-born infant(s) • Are not participating in a teriflunomide clinical trial at time of pregnancy exposure
Exclusion criteria	**Teriflunomide-exposed pregnant women with MS who:** • Do not receive health care in a country where a registry is operational • Were participating in a clinical trial investigating teriflunomide at time of pregnancy exposure

[a]If a National Coordinator determines that a patient is not eligible, all completed forms will be sent to the Registry Coordinating Centre for tracking purposes; these cases will not be entered into the registry database

Table 2. Study Objectives

Primary objective	• Compare rate of birth defects in teriflunomide-exposed pregnant women with those reported by the population-based European surveillance system, EUROCAT[10]
Secondary objective	• Compare rate of birth defects in teriflunomide-exposed pregnant women with those reported by the population-based US surveillance system, MACDP[12] • Estimate proportions of pregnancy outcomes, including live-born infants, in teriflunomide-exposed pregnant women • Estimate proportions of preterm live births (<37 weeks of gestation) among live-born infants of teriflunomide-exposed pregnant women • Estimate proportions of alterations in foetal/infant growth, indications of delayed development, and functional deficits observed during first year of life in live-born infants of teriflunomide-exposed pregnant women

EUROCAT=European Surveillance of Congenital Anomalies; MACDP=Metropolitan Atlanta Congenital Defects Program

Table 3. Registry Information Collation[11]

Maternal information	• Demographics • Current pregnancy information (LMP, EDD, age at conception) • Obstetric history, including history of birth defects • Family history of birth defects (maternal/paternal) • Concomitant medications and other exposures • Teriflunomide and accelerated elimination procedure (agent dosage, duration, results), pregnancy attribution • Concurrent acute or chronic medical conditions during pregnancy, including MS (history and status) • Prenatal tests (type, gestational age, results)
Pregnancy outcome	• Live birth • Spontaneous abortion (<20 weeks of gestation) • Foetal death (≥20 weeks of gestation) • Induced abortion without evidence of birth defects • Termination of pregnancy for foetal anomaly after prenatal diagnosis • Ectopic pregnancy • Molar pregnancy • Neonatal (28 days after live birth) or maternal (during pregnancy or at time of delivery) death
Birth defects	• Birth defects will be classified according to EUROCAT[10] and MACDP[12] conventions, and reviewed by the Registry's birth defect evaluator
Infant characteristics	• Observed during first year of life, including prematurity and serious adverse outcomes

EDD=estimated date of delivery; LMP=first day of last menstrual period.

RESULTS

- As of August 2019, 32 patients have been enrolled from 8 countries
- As of August 2019, there have been 22 live births

References

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Teriflunomide is approved in many countries, including the US and the European Union, for the treatment of relapsing multiple sclerosis or relapsing-remitting multiple sclerosis. This material may contain information that is outside of the approved labelling in some countries.