Teriflunomide (Aubagio®) International Pregnancy Registry: Enrolment Update

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OBJECTIVE

- **To provide the study design and updated enrolment for the International Teriflunomide Pregnancy Exposure Registry**

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved for the treatment of patients with relapsing forms of MS in over 80 countries, including the United States and countries of the European Union. As of August 2018, over 93,000 patients were being treated with teriflunomide, with a total real-world exposure of approximately 186,000 patient-years as of December 2017
- In addition to a consistent, well-characterised safety and tolerability profile,[1–4] teriflunomide has demonstrated consistent efficacy on clinical and MRI disease activity in patients with relapsing forms of MS[1–3] and in those who experienced a first clinical episode suggestive of MS[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]
  - Rats exhibit greater sensitivity to the effects of teriflunomide than humans, which may explain why similar plasma exposures of teriflunomide have resulted in teratogenicity in animals but not, to date, in humans[6]
- 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[7] for the treatment of rheumatoid arthritis)
  - A prospective study conducted by the Organization of Teratology Information Specialists (OTIS) 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.[8] These observations were confirmed in a subsequent OTIS case series[9]
- Despite the requirement for contraceptive use, a number of pregnancies were reported during the teriflunomide clinical trial program
- Although there is no evidence of a signal for teratogenicity or other adverse outcomes, it is important to collect data regarding teriflunomide exposure in pregnancy to evaluate any potential adverse outcomes[10]
- Global teriflunomide pregnancy registries have been established and will capture prospective data from pregnancies within the postmarketing setting
- **Table 1** outlines the primary and secondary objectives of the registry

Table 1. International Teriflunomide Pregnancy Exposure Registry Objectives

Primary objective	• Compare rate of birth defects in teriflunomide-exposed pregnant women with those reported by the population-based European surveillance system, EUROCAT[12]
Secondary objectives	• Compare rate of birth defects in teriflunomide-exposed pregnant women with those reported by the population-based US surveillance system, MACDP[13] • 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.

METHODS

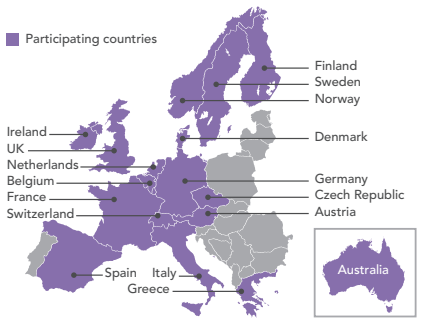
Registry Design

- The registry is an ongoing, voluntary, multinational, prospective, observational, exposure-registration study operating in the following countries:
  - Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, and the United Kingdom (**Figure 1**)
- National Coordinators liaise with healthcare professionals (HCPs) to collect information on teriflunomide-exposed pregnancies and oversee enrolment in the registry

CONCLUSIONS

- **The International Teriflunomide Pregnancy Exposure Registry will provide outcomes on teriflunomide-exposed pregnancies, in addition to 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**

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



- To maximise recruitment, an open-enrolment approach is employed, with participation available to all eligible women through reporting HCPs, such as obstetricians, neurologists, and general practitioners
- The registry design and inclusion/exclusion criteria are shown in **Figure 2** and **Table 2**, respectively

Figure 2. Registry Design[11]

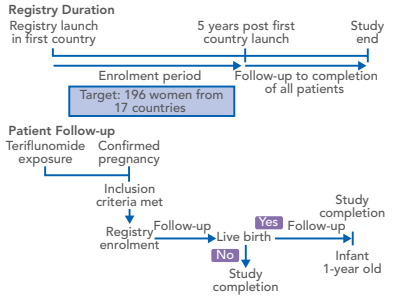


Table 2. Inclusion and Exclusion Criteria[11a]

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 healthcare in the participating countries (shown above) • 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 healthcare 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 Center for tracking purposes. These cases will not be entered into the registry database.

Patient Enrolment

- Once a new teriflunomide-exposed pregnancy is reported, HCPs seek to obtain the potential participant's consent to pass their details onto the co-ordinating study centre, who then assess patient eligibility for enrolment in the registry
- To enrol a patient, HCPs can contact the National Coordinating Centre in their country

Outcomes

- Pregnancy outcomes in addition to infant characteristics during the first year of life are being collected (**Table 3**)

Table 3. International Teriflunomide Pregnancy 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[12] and MACDP[13] conventions, and reviewed by the Registry's birth defect evaluator
Infant characteristics	• Infant characteristics, including prematurity and serious adverse outcomes, observed during first year of life

EDD, estimated date of delivery; EUROCAT, European Surveillance of Congenital Anomalies; LMP, first day of last menstrual period; MACDP, Metropolitan Atlanta Congenital Defects Program.

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[12]
- Analyses will be based on prospective cases of women with teriflunomide exposure during pregnancy prior to the knowledge, or perceived knowledge, of pregnancy outcome (ie, structural defect or genetic abnormality noted on a prenatal test) and will be conducted in 3 populations —the primary analysis population, pregnant women, and live infants:
  - **Primary analysis population:** Eligible pregnant women with available pregnancy outcomes and birth-defect status of any live-born infant(s) available at birth or 1-year follow-up. Used for evaluation of primary objective and rate of birth defect (secondary objective)
  - **Pregnant women 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 women 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 reviewed carefully by the Registry and summarised separately in interim and final reports)
- Teriflunomide pregnancy exposure data will be classified by gestational week and trimester

RESULTS

- Patient enrolment commenced in early 2015 and is planned to continue until December 2019
- Interim data have been collected from the registry:
  - As of 23 July 2018, 22 patients have been recruited from 8 countries
  - Outcomes are available for 18 pregnancies at the interim analysis, with a cutoff date of 23 July 2018
    - There have been 16 live births
    - There were no abnormalities reported among 15 of the 16 live births. There was one case of ectopic heartbeat, identified prospectively
    - One patient in Spain had an elective termination that was not motivated by the abnormal result of a prenatal test or by any suspicion of a potential birth defect
  - One serious adverse event was reported in a retrospective case:
    - Reported as death of one of twin foetuses (in utero) as possibly related to teriflunomide exposure, with the subsequent spontaneous abortion per physiopathology as not related to teriflunomide exposure
    - The surviving twin was delivered prematurely, with no abnormalities reported to date

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