Teriflunomide (AUBAGIO®) Pregnancy Registry: Design and Enrolment Procedures for Pregnant Women With Multiple Sclerosis Exposed to Teriflunomide

David Rog,[1] Kerstin Hellwig,[2] Christine Lebrun-Frenay,[3] Diane Daniel,[1] Nicola Seferta,[1] Myriam Benamor,[4] Stéphanie Tcherny-Lessenot,[5] Philippe Truffinet,[4] Angelo Ghezzi[6]

[1]Greater Manchester Neurosciences Centre, Salford Royal NHS Foundation Trust, Salford, UK; [2]St Josef Hospital, Ruhr University Bochum, Bochum, Germany; [3]Department of Neurology, Hôpital Pasteur, Nice, France; [4]Genzyme, a Sanofi company, Chilly-Mazarin, France; [5]Sanofi, Chilly-Mazarin, France; [6]Ospedale di Gallarate, Gallarate, Italy

OBJECTIVE

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

INTRODUCTION

- Teriflunomide is a once-daily oral immunomodulator approved in the UK for active relapsing-remitting MS
- Teriflunomide has demonstrated consistent efficacy on clinical disease activity and magnetic resonance imaging endpoints in patients with relapsing forms of MS[1-3] and in those who experienced a first clinical episode suggestive of MS.[3] Teriflunomide also has a consistent and well-characterized safety and tolerability profile[1-4]
- Teriflunomide is contraindicated in pregnant women and women of childbearing potential not using reliable contraception, based on the occurrence of teratogenicity and embryo toxicity in the offspring of teriflunomide-treated rats and rabbits[5]
- Teriflunomide is the principal active metabolite of leflunomide (approved for treatment of rheumatoid arthritis since 1998[6])
  - In a prospective study by the Organization of Teratology Information Specialists (OTIS), there were no significant differences in the rate of major structural defects and no pattern of major or minor anomalies in newborns of women exposed to leflunomide compared with disease-matched or healthy comparator groups.[7] These observations were confirmed in a subsequent OTIS analysis[8]
- During the teriflunomide clinical trial programme, despite the requirement for contraceptive use, a number of pregnancies were reported
  - While there were no signs of structural or functional abnormalities in newborns of women or partners of men exposed to teriflunomide during pregnancy, it is important to collect data regarding teriflunomide exposure in pregnancy to evaluate any potential adverse outcomes[9]
- Global teriflunomide pregnancy registries have been established and will capture prospective data from pregnancies in the post-marketing setting

METHODS

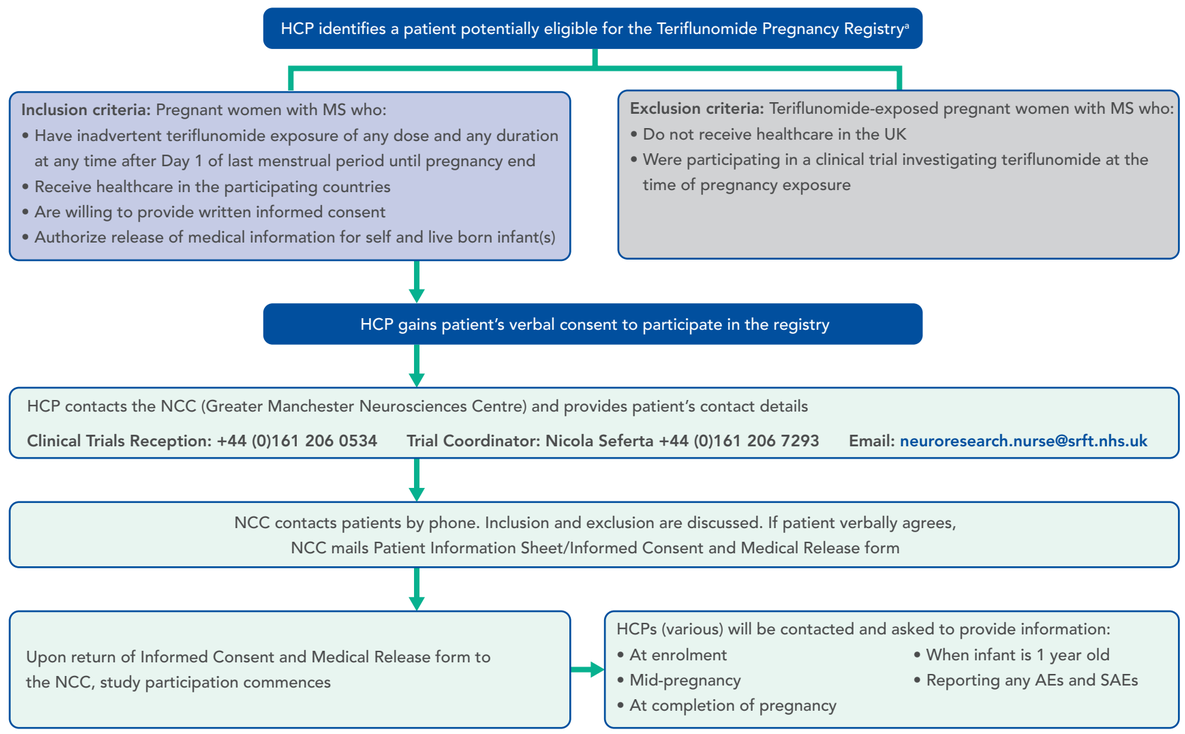
Registry Design

- The registry is a voluntary, multinational, prospective, observational, non-interventional, exposure-registration study operating in the following countries:
  - EU: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Ireland, Italy, the Netherlands, Norway, Spain, Sweden and the UK
  - Switzerland
  - Australia
- National coordinators will liaise with healthcare professionals to collect information on teriflunomide-exposed pregnancies and coordinate and encourage patient enrolment in the registry (**Figure 1**)
  - UK healthcare professionals wishing to submit information relating to teriflunomide-exposed pregnancies to the registry should contact the National Coordinating Centre, Manchester, UK (neuroresearch.nurse@srft.nhs.uk)
- The registry design is shown in **Figure 2**

CONCLUSIONS

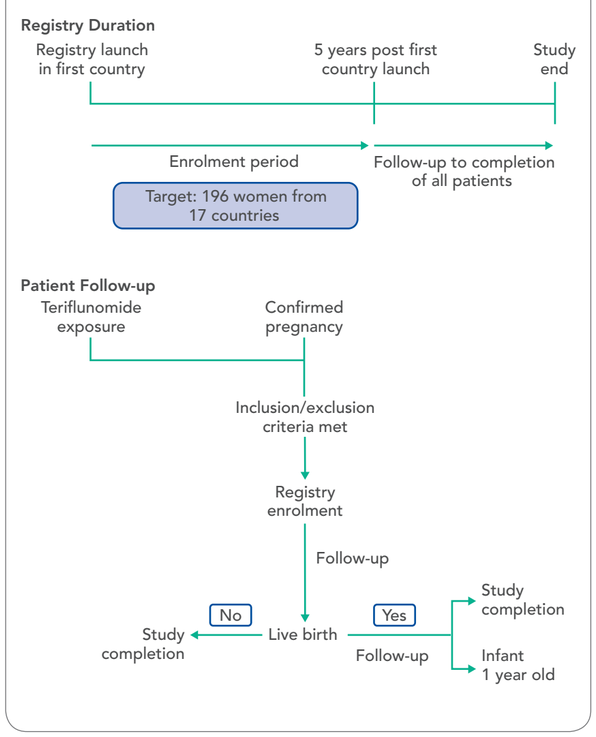
- **This registry aims to monitor and provide data on pregnancy outcomes and infant health, growth and development during the first year of life in infants born to women who were inadvertently exposed to teriflunomide during their pregnancy**
- **The findings from this registry, along with those from a US/Canadian teriflunomide pregnancy exposure registry, will help physicians provide better counselling for women exposed to teriflunomide during pregnancy**

Figure 1. Procedure for Patient Referral and Enrolment in the Teriflunomide Pregnancy Exposure Registry in the UK



[a]Early pregnancy enrolments are preferred to minimize bias associated with prenatal testing. AE, adverse event; HCP, healthcare professional; NCC, National Coordinating Centre; SAE, serious AE.

Figure 2. Registry Design



Outcomes

- The registry will allow collation of maternal information and information on pregnancy outcomes, birth defects and infant characteristics (**Table 1**)
- The primary and secondary study objectives are outlined in **Table 2**

Statistical Analysis

- The registry will recruit 196 women to achieve 104 live births, providing 80% power to detect a 3.95-fold increase in the risk ratio of birth defects associated with teriflunomide exposure vs EUROCAT birth defect rates
- Analyses of primary and secondary objectives (**Table 2**) will be based on prospective cases, including cases registering teriflunomide exposure during pregnancy prior to knowledge or perceived knowledge of pregnancy outcome (i.e. structural defect or genetic abnormality noted on a prenatal test)
- There will be 3 analysis populations:
  - **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
- Teriflunomide pregnancy exposure data will be classified by gestational week and trimester

Table 1. Teriflunomide Pregnancy Exposure Registry Information Collation

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 following 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[11] 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.

Table 2. Study Objectives

Primary objectives	Compare rate of birth defects in teriflunomide-exposed pregnant women with those reported by the population-based European surveillance system, EUROCAT[10]
Secondary objectives	Compare rate of birth defects in teriflunomide-exposed pregnant women with those reported by the population-based US surveillance system, MACDP[11]
	Estimate proportions of pregnancy outcomes in teriflunomide-exposed pregnant women
	Estimate proportions of pre-term 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.

RESULTS

- Enrolment began in early 2015 and will continue for approximately 5 years
- Interim results will be reported when available
- HCPs referring patients and contributing information to the Registry will be duly acknowledged

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Acknowledgements and Disclosures

This poster was reviewed by Larisa Miller, PharmD, of Genzyme, a Sanofi company. Editorial support for this poster was provided by Steve Banner, of Fishawack Communications, and was funded by Genzyme.

DR: Consulting fees (Bayer Schering, Biogen Idec, Merck Serono, Novartis, Roche, Sanofi, Teva Neuroscience); research support (Biogen Idec, Genzyme, GW Pharma, Merck Serono, Mitsubishi, Novartis, Teva Neuroscience). **KH:** Consulting fees, honoraria or scientific committee support (Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi, Teva). **CL-F:** Consulting fees, honoraria or scientific committee support (Allergan, Almirall, Bayer Schering, Biogen Idec, Genzyme, Merck Serono, Novartis, Sanofi, Teva). **DD:** Nothing to disclose. **NS:** Nothing to disclose. **MB:** Employee of Genzyme. **ST-L:** Employee of Sanofi. **PT:** Employee of Genzyme, with ownership interest. **AG:** Honoraria for consultancy (Biogen Idec, Merck Serono); travel grants or grants as speaker (Merck Serono, Novartis, Sanofi/Genzyme, Teva Neuroscience).

Data included in this poster were previously presented at the following meetings: EAN, June 20–23, 2015, Berlin, Germany; MS Frontiers, June 29–30, 2015, London, UK; and DGN, September 23–26, 2015, Düsseldorf, Germany.

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.

Presented at MS Trust Annual Conference, November 8–10, 2015, Nr. Windsor, UK
Funding provided by Genzyme, a Sanofi company