OBJECTIVE

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

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

INTRODUCTION

Teriflunomide is a once-daily oral immunomodulator approved in the UK for active relapsing-remitting MS

Teriflunomide has demonstrated clinical disease activity and magnetic resonance imaging endpoints in patients with relapsing forms of MS1-3 and in those who experienced a first clinical episode suggestive of MS.2 Teriflunomide also has a consistent and well-characterized safety and tolerability profile.4-14

Teriflunomide is contraindicated in pregnant women and women of childbearing potential not able to reliably contrasept, based on the occurrence of teratogenicity and embryo toxicity in the offspring of teriflunomide-treated rats and rabbits5-7.

Teriflunomide is the principal active metabolite of leflunomide (approved for treatment of rheumatoid arthritis since 1998).8

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.9 These observations were confirmed in a subsequent OTIS analysis.10

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 prospective data regarding teriflunomide exposure in pregnancy to evaluate any potential adverse outcomes11

• 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@surf.nhs.uk)

The registry design is shown in Figure 2

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

Comparative 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

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