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4-Year Interim Enrolment Results of LEMTRADA® (Alemtuzumab) Pregnancy Exposure Registry

David Rog[1], Tatiana Mihalova[1], Yang Zhao[2], Tanya Fischer[2], David H Margolin[2]

[1]Salford Royal NHS Foundation Trust, Salford, UK; [2]Sanofi, Cambridge, MA, USA

OBJECTIVE

- **To report study design and 4-year interim enrolment results for the International LEMTRADA® (Alemtuzumab) Pregnancy Exposure Registry**

INTRODUCTION

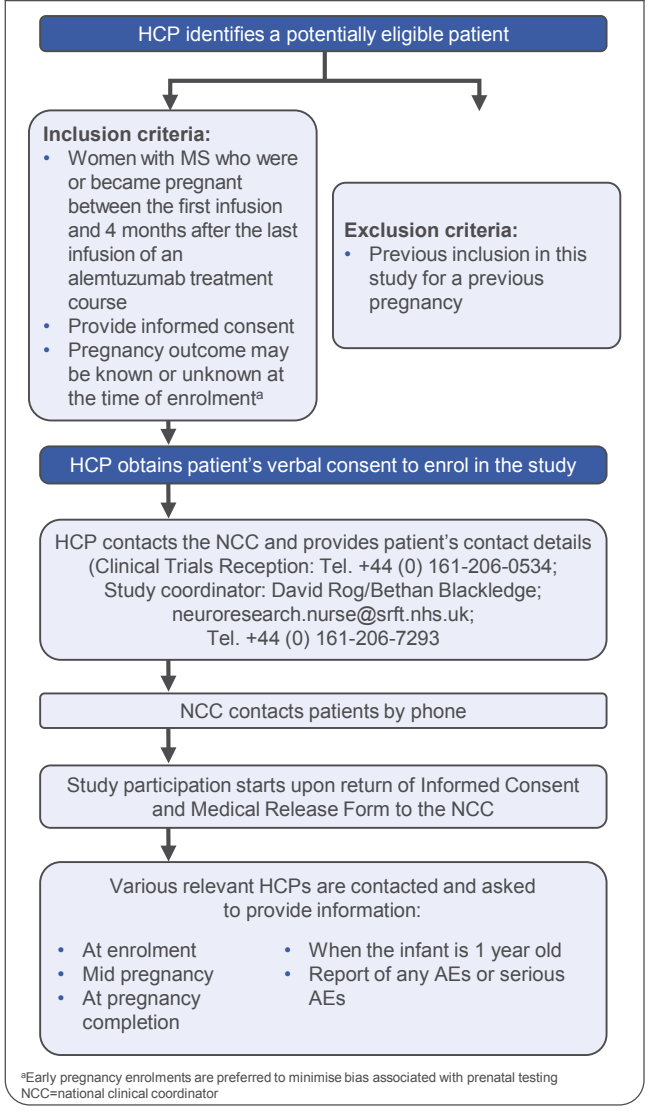
- In phase 2 and 3 studies of patients with RRMS (NCT00050778; NCT00530348; and NCT00548405), alemtuzumab demonstrated significantly greater improvements on clinical and MRI outcomes versus subcutaneous interferon beta-1a over 2 or 3 years, and efficacy was maintained over an additional 7 years in 2 consecutive extension studies (NCT00930553; NCT02255656)[1-7]
- Adverse events (AEs) associated with alemtuzumab treatment in clinical trials and postmarketing experience include infusion-associated reactions, increased frequency of infection and the potential for opportunistic infections, secondary autoimmunity (thyroid disorders, immune thrombocytopaenia, nephropathies, autoimmune cytopaenias, autoimmune hepatitis, and other less common autoimmune events), acute acalculous cholecystitis, and cardiovascular and pulmonary events possibly related to infusion[1-8]
- Alemtuzumab concentration is low or undetectable in human serum within approximately 30 days after administration,[9] yet it is recommended that women of childbearing potential use contraception during and for 4 months after treatment to reduce the likelihood of exposure to the foetus[8]
- There was no evidence of malformations in animals treated with alemtuzumab during gestation, and development was not affected in murine pups exposed to alemtuzumab during lactation[8]
- Data from pregnancies occurring during the alemtuzumab clinical trials do not suggest an increased risk of adverse pregnancy outcomes[10]

METHODS

Registry Design

- This is a voluntary, international, prospective, noninterventional, observational, postauthorisation safety study conducted in Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Mexico, the Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, UK, and USA
- National coordinators will liaise with health care professionals (HCPs) to collect data on alemtuzumab-exposed pregnancies and coordinate and encourage patient enrolment in the registry (**Figure 1**)
- The registry design is depicted in **Figure 2**

Figure 1. Procedure for Patient Referral and Enrolment



[a]Early pregnancy enrolments are preferred to minimise bias associated with prenatal testing
NCC=national clinical coordinator

CONCLUSIONS

- **The ongoing enrolment of women exposed to alemtuzumab during pregnancy will provide valuable data on pregnancy outcomes and development in infants with potential exposure to alemtuzumab**
- **The findings will generate more data about women exposed to alemtuzumab during pregnancy, as the study's outcomes will be compared with external cohorts of women with MS who have not been exposed to alemtuzumab during pregnancy, as well as pregnant women without MS**

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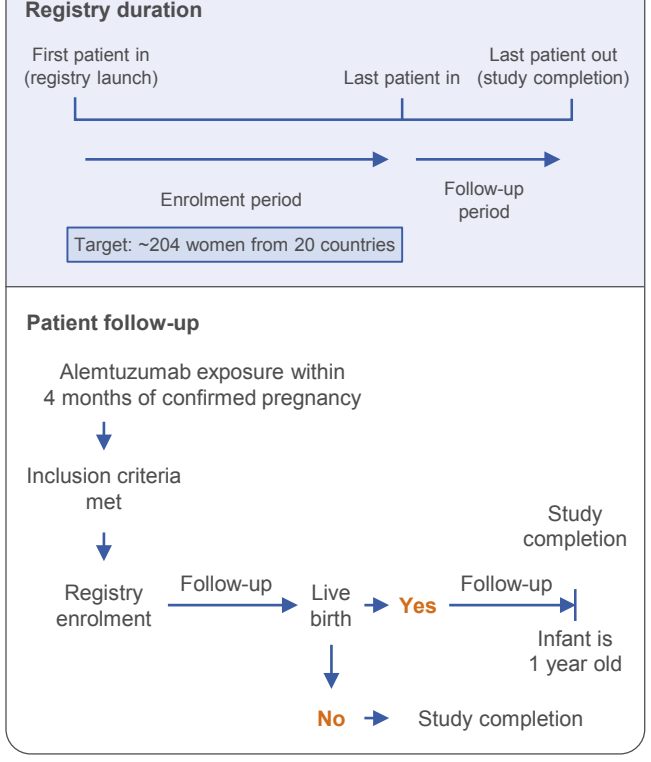
Figure 2. Registry Design



Outcomes

- The International LEMTRADA® (Alemtuzumab) Pregnancy Exposure Registry will collate maternal information, as well as information on pregnancy outcomes, birth defects, and infant health status up to 1 year of age (**Table 1**)
- Data are collected via interview during each trimester, and within 6 weeks after delivery or end of pregnancy

Statistical Analysis

- The registry will recruit approximately 204 women who were exposed to alemtuzumab during pregnancy to obtain 1-year postdelivery follow-up data from approximately 193 women
  - This sample size will provide 80% power (with a 1-sided, 2-sample test significance level of 0.025) to detect a 2-fold higher relative risk ratio of birth defects in women with MS exposed to alemtuzumab during pregnancy, compared with external cohorts of women with MS who have not been exposed to alemtuzumab during pregnancy, as well as pregnant women without MS
- Analyses of primary and secondary objectives (**Table 2**) will be based on prospective cases, although pregnant women may be enrolled who are later determined to be retrospective cases (eg, if information suggestive of abnormality is available before the initial registration date)
- Analysis populations
  - Primary analysis population:
    - Eligible pregnant women with available pregnancy outcome data and health status of any live-born infant(s) available at birth or 1-year follow-up
  - Secondary analysis populations for descriptive analyses of baseline characteristics:
    - All enrolled women, including those whose pregnancy outcome data are unknown
    - Subset of women whose pregnancy outcome data are unknown will also be calculated
  - Secondary analysis population for analyses of infant characteristics:
    - All live-born infants from the pregnant women population

Table 1. Information Collation

Maternal information	• Demographics • Targeted medical history, including concurrent medical conditions and prior treatment for MS • Family history of birth defects • History and outcome of previous pregnancies • Current pregnancy information • Prenatal tests: type, gestational age, and results (if applicable) • Risk factors: smoking, alcohol use, illicit drug use, and prepregnancy alemtuzumab exposure (infusion dates) • Concomitant medications • Other characteristics: weight gain, gestational age at delivery, mode of delivery, type/length of hospital stay, and complications
Pregnancy outcome	• Spontaneous abortion (≤20 weeks of gestation; primary endpoint) • Foetal death/stillbirth (>20 weeks of gestation)[a] • Foetal major malformations • Preterm birth • Small size for gestational age at birth and up to 1 year of age • Live birth • Induced abortion without evidence of birth defects • Termination of pregnancy due to foetal abnormality (per prenatal diagnosis) • Neonatal (28 days after live birth) or maternal (during pregnancy or delivery) death[a] • Lost to follow-up
Birth defects	• Classified per the EUROCAT and MACDP conventions[11,12]
Infant characteristics	• Gender, weight, length, Apgar score, head circumference, prematurity, complications, and serious adverse outcomes observed up to 1 year of age

[a]For stillborn infants, information about the gender, birth size, and presence/absence of structural defects is/will be collected, along with pathology and autopsy results if available
EUROCAT=European Surveillance of Congenital Anomalies; MACDP=Metropolitan Atlanta Congenital Defects Program

Table 2. Study Objectives

Primary objective	To evaluate pregnancy outcomes in women with MS who became pregnant within 4 months after alemtuzumab exposure, and to determine if the risk of any adverse pregnancy outcomes in these women is higher compared with external cohorts of women with MS who have not been exposed to alemtuzumab during pregnancy, as well as pregnant women without MS
Secondary objective	To further characterise prenatally exposed live births including assessment of outcomes in the neonatal and paediatric periods for up to 1 year of age (pending available data)

RESULTS

- As of September 2019, 19 countries have open sites
- 38 pregnant women from 11 countries have enrolled in the registry

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Previously presented at the at the 21st Annual Conference of the MS Trust (MST), 12–14 November 2017, Hinckley, United Kingdom
Alemtuzumab is approved in >70 countries for treatment of adults with relapsing forms of multiple sclerosis (MS). In the EU, the European Medicines Agency has issued a provisional measure that, at the moment, new treatment should only be initiated in adult patients with highly active relapsing-remitting multiple sclerosis despite a full and adequate course of treatment with at least two other disease-modifying treatments, or in adult patients with highly active relapsing-remitting multiple sclerosis where all other disease-modifying treatments are contraindicated or otherwise unsuitable. In the US, the indication provides that, because of its safety profile, the use of alemtuzumab should generally be reserved for patients who have had an inadequate response to 2 or more drugs indicated for the treatment of MS. This material may contain information that is outside of the approved labelling in some countries.

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