LEMTRADA® (Alemtuzumab) Pregnancy Exposure Registry: Study Design and Enrolment Procedures for Pregnant Women With Multiple Sclerosis Exposed to Alemtuzumab

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OBJECTIVE

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

CONCLUSIONS

- **This registry of women exposed to alemtuzumab during pregnancy will provide valuable data on pregnancy outcomes and infant health, growth, and development in the first year of life**
- **The findings will help provide more data to healthcare professionals 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**
- **The LEMTRADA® Pregnancy Registry is now open to enrolment**

INTRODUCTION

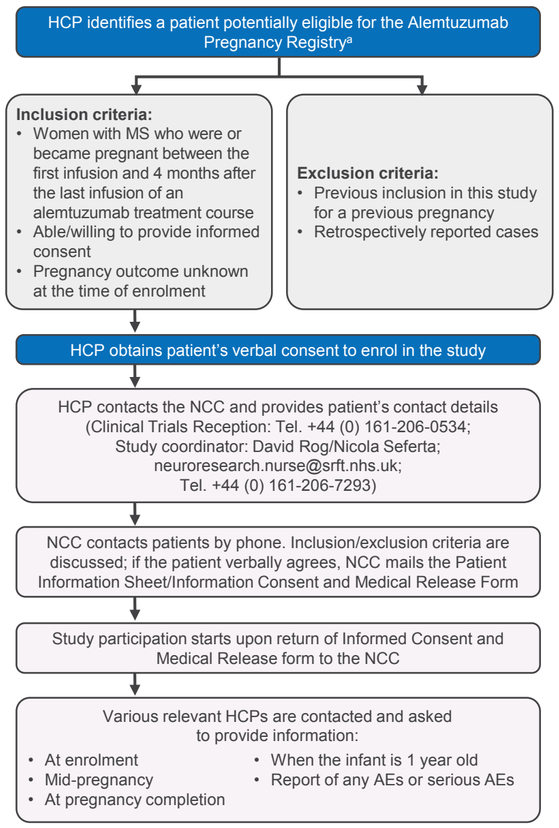
- Alemtuzumab (LEMTRADA®; Genzyme) is a humanised anti-CD52 monoclonal antibody administered as 2 courses, infused on 5 days at initiation of treatment and on 3 days 12 months later, and approved in over 45 countries for the treatment of patients with relapsing-remitting MS (RRMS), resulting in depletion and subsequent repopulation of circulating T and B lymphocytes[1-5]
- Patients demonstrated greater improvements on clinical and MRI outcomes with alemtuzumab compared with SC IFNB-1a in phase 2 and 3 studies of patients with active RRMS[6-8]
  - Alemtuzumab had durable efficacy over 5 years in an ongoing, open-label extension study[9,10]
- The most frequent adverse events (AEs) with alemtuzumab were infusion-associated reactions; other AEs of interest included autoimmune AEs[7,8]
- There are no clinical studies of alemtuzumab in pregnant women; however, because MS is frequently diagnosed in women of childbearing age, it is important to assess the effects of disease-modifying therapy on pregnancy
- There was no evidence of malformations in animals treated with alemtuzumab during gestation[11]
  - Moreover, cognitive, physical, and sexual development were not affected in murine pups exposed to alemtuzumab at higher doses during lactation[11]
- Although alemtuzumab is low or undetectable in human serum within approximately 30 days after administration,[4] 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[11]
- During the phase 2 and 3 alemtuzumab clinical trials, despite a requirement for contraceptive use, a number of pregnancies were reported[12]
  - There has been no teratogenicity signal in delivered infants[12]
  - Spontaneous abortion risk was comparable with rates in treatment-naive MS patients and the general population[12]

METHODS

Registry Design

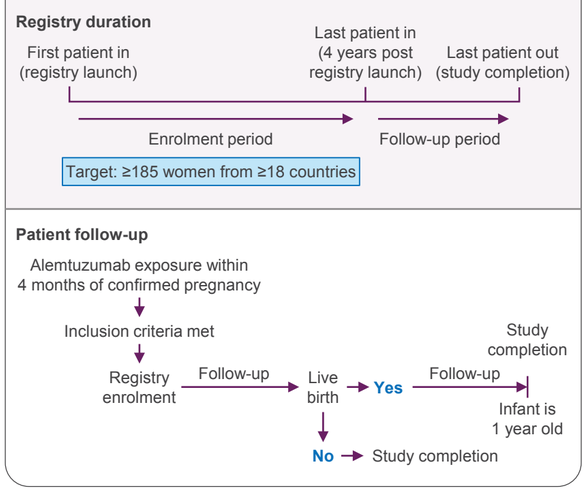
- This is a voluntary, international, prospective, noninterventional, observational, post-authorisation safety study conducted in the following countries:
  - Australia, Austria, Belgium, Canada, Denmark, Finland, France, Germany, Ireland, Italy, Mexico, Netherlands, Norway, Poland, Portugal, Spain, Sweden, Switzerland, and the UK
  - Additional countries may be added
- National coordinators will liaise with healthcare professionals (HCPs) to collect data on alemtuzumab-exposed pregnancies and coordinate and encourage patient enrolment in the registry (**Figure 1**)
- UK HCPs wishing to submit information related to alemtuzumab-exposed pregnancies should contact the National Coordinating Centre (NCC; Manchester, UK): Neuroresearch.nurse@srft.nhs.uk
- The registry design is depicted in **Figure 2**

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



[a]Early pregnancy enrolments are preferred to minimise bias associated with prenatal testing

Figure 2. Registry Design



Outcomes

- The 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

Table 1. Alemtuzumab Pregnancy Registry Information Collation

Maternal information	• Demographics • Targeted medical history, including concurrent medical conditions (acute or chronic) and prior treatment for MS • Family history of birth defects • History of previous pregnancies: outcome of each, complications, foetal/neonatal abnormalities and type • Current pregnancy information: fertility treatment (if applicable), LMP, EDD, age at conception, and status • 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: OTC, prescription medications, vitamin supplements (including folic acid), herbal medicines from the date of enrolment • Other characteristics: weight gain, gestational age at delivery, mode of delivery, type/length of hospital stay, and complications
Pregnancy outcome	• Live birth • Preterm birth • Foetal major malformations • Spontaneous abortion (≤20 weeks of gestation) • Foetal death/stillbirth (>20 weeks of gestation) • Induced abortion without evidence of birth defects • Termination of pregnancy due to foetal abnormality (per prenatal diagnosis) • Small size for gestational age at birth and up to 1 year of age • Neonatal (28 days after live birth) or maternal (during pregnancy or delivery) death[a] • Lost to follow-up (if pregnancy outcome is not available within 1 year of EDD despite several attempts to obtain the information)
Birth defects	• Classified per the EUROCAT and MACDP conventions[13,14]
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
EDD=estimated date of delivery; EUROCAT=European Surveillance of Congenital Anomalies; LMP=first day of the last menstrual period; MACDP=Metropolitan Atlanta Congenital Defects Program; OTC=over-the-counter

Statistical Analysis

- The registry will recruit ≥185 women who were exposed to alemtuzumab during pregnancy to obtain 1-year post-delivery follow-up data from approximately 150 women
  - This sample size will provide 80% power (with a 2-sided significance level of 0.05) to detect a 2- to 4-fold higher 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 liveborn 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 liveborn infants from the pregnant women population

Table 2. Study Objectives

Primary objective	To evaluate pregnancy outcomes in women with MS who became pregnant within 4 months after alemtuzumab infusion and 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 pediatric periods for up to 1 year of age (pending available data)

RESULTS

- The study is currently open for enrolment and will continue for approximately 4 years
  - As of October 2015, 1 patient has enrolled in the study

References

1. Hu Y, Turner MJ, Shields J, et al. *Immunology* 2009;128:260-70. 2. Havari E, Turner MJ, Campos-Rivera J, et al. *Immunology* 2014;141:123-31. 3. Kasper LH, Arnold DL, Coles AJ, et al. *Mult Scler* 2013;19:P531. 4. Kovarova I, Arnold DL, Cohen JA, et al. Presented at: ENS; June 9-12, 2012; Prague, Czech Republic, P341. 5. Cox AL, Thompson SA, Jones JL, et al. *Eur J Immunol* 2005;35:3332-42. 6. CAMMS223 Trial Investigators, Coles AJ, Compston DA, et al. *N Engl J Med* 2008;359:1786-801. 7. Cohen JA, Coles AJ, Arnold DL, et al. *Lancet* 2012;380:1819-28. 8. Coles AJ, Twyman CL, Arnold DL, et al. *Lancet* 2012;380:1829-39. 9. Havrdova E, Arnold DL, Cohen JA, et al. *Mult Scler* 2015;23:152. 10. Fox EJ, Arnold DL, Cohen JA, et al. *Mult Scler* 2015;23:P1102. 11. LEMTRADA Summary of Product Characteristics. United Kingdom: Genzyme Therapeutics, Ltd.; 2013. 12. Achiron A, Chambers C, Fox EJ, et al. *Mult Scler* 2015;23:P1120. 13. European Surveillance of Congenital Anomalies. Guide 1.3 and reference documents, 2013. http://www.eurocat-network.eu/content/EUROCAT-Guide-1.3.pdf. Accessed Oct 13, 2015. 14. Centers for Disease Control and Prevention. Birth Defects and Genetic Diseases Branch 6-Digit Code for Reportable Congenital Anomalies, 2007. http://www.cdc.gov/ncbddd/birthdefects/documents/ macdpcode0807.pdf. Accessed Oct 13, 2015.

Acknowledgements and Disclosures

This poster was reviewed by Aji Nair and Sarah Strattman of Genzyme, a Sanofi company. Editorial support for the poster was provided by Susan M Kaup, PhD, and Michele Jacob, PhD, Evidence Scientific Solutions, 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). **NS, DD,** and **TM:** Nothing to disclose. **MR, SC, YZ, TF, DHM,** and **MAP:** Employees of Genzyme.

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