AMENDED CLINICAL TRIAL PROTOCOL 02

COMPOUND: LEMTRADA

International LEMTRADA Pregnancy Exposure Cohort in Multiple Sclerosis

STUDY NUMBER: OBS13436

VERSION DATE / STATUS: 16-Nov-2016 / Approved

The Study is conducted by INC Research, hereinafter referred also as the MAH representative

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PASS Information

Title	International LEMTRADA Pregnancy Exposure Cohort in Multiple Sclerosis
Protocol version identifier	1 electronic 2.0
Date of last version of protocol	29-Oct-2014
EU PAS register number	ENCEPP/SDPP/ 7574
Active substance	Alemtuzumab
Medicinal product	LEMTRADA
Product reference	EU/1/13/869/001
Procedure number	EMEA/H/C/003718
Marketing authorization holder(s)	Genzyme Therapeutics, Ltd
Joint PASS	No
Research question and objectives	This post authorization safety study (PASS) is an international, observational cohort study (registry) of pregnancy outcomes in women with multiple sclerosis (MS) exposed to LEMTRADA during pregnancy. Pregnancy outcomes in women exposed to LEMTRADA will be compared with available data from external comparison groups: women with MS not exposed to LEMTRADA, and women without MS. This is an observational study with no experimental intervention utilized. Women enrolled in the study may receive treatment and evaluations for their MS and their pregnancies as determined by their treating physicians in accordance with local standard of care. Both prospective and retrospective (exposed to LEMTRADA during pregnancy but the pregnancy outcome known at time of registry) data are collected but analyzed separately. Information of prospective pregnancies will be collected during each trimester and within 6 weeks after the end of pregnancy. For all live births, the infant's Health Care Provider (HCP) will be contacted at 1 year post-delivery to obtain follow-up on the infant's health status. The total duration of the study is expected to be approximately 5 years, with study recruitment expected to be 4 years. The main objective of this registry is to assess maternal, fetal and infant outcomes in women exposed to LEMTRADA during pregnancy. The registry will detect and record: Primary outcome: spontaneous abortion Secondary outcomes: major and minor congenital malformations, pregnancy outcome (stillbirth, elective termination, preterm birth, full-term live birth), small for gestational age at birth, any other adverse pregnancy outcomes. For the prospectively collected cases, these outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through the first year of life. Retrospectively collected cases of each outcome will be qualitatively described by maternal and pregnancy characteristics as well as timing of LEMTRADA exposure.
Country(-ies) of study	North America (NA), Europe (EU) and rest of the world (ROW).

Author	[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Genzyme Therapeutics, Ltd
MAH/MAH REPRESENTATIVE contact person (Qualified Person responsible for Pharmacovigilance, QPPV)	[redacted]

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2 LIST OF ABBREVIATIONS

AE:	adverse event
BDE:	Birth Defect Evaluator
CI:	confidence intervals
CRFs:	Case Report Forms
FDA:	Food and Drug Administration
GD:	Gestation Day
GEP:	Good Epidemiology Practice
HCPs:	health care providers
huCD52:	human CD52
ICF:	Informed Consent Form
IEC:	Independent Ethics Committee
IgG:	human immunoglobulin G
IRB:	Institutional Review Board
MAH:	Marketing Authorization Holder
MS:	multiple sclerosis
PASS:	post authorization safety study
SAEs:	serious adverse events

3 RESPONSIBLE PARTIES

The execution of this protocol is the responsibility of the following parties:

- Marketing Authorization Holder (MAH),
- Clinical Research Organization (CRO) (MAH representative)
- National Coordinators for each country in which the study (registry) is operational,
- Scientific Advisory Committee.

3.1 MARKETING AUTHORIZATION HOLDERS

Marketing Authorization Holder oversees the activities of CRO, meets regulatory reporting responsibilities which includes the submission of the protocol, where required by national regulations, for Health Authority/Ministry of Health approval, and facilitates Competent Authority submissions.

3.2 MAH REPRESENTATIVE

The MAH Representative for this study is INC RESEARCH) (based in North Carolina, USA), a contract research organization delegated to serve as the Study (registry) Coordinating Centre. The MAH Representative is responsible for the operational conduct of the study including recruiting, training, and quality control of the National Coordinators throughout the duration of the study, facilitating data collection through the National Coordinators, ensuring adherence to local regulations including data privacy, and overseeing the work of the National Coordinators. In addition, the MAH/CRO will perform the statistical analyses, draft the study reports and other study documents.

3.3 NATIONAL COORDINATORS

Each country will have a National Coordinator (a physician appointed by the Study Coordinating Centre) responsible for the conduct of the study in his or her country. The National Coordinators' responsibilities include obtaining required approvals from Ethics Committees, facilitating the collection of study data through health care providers (HCPs), confirming the eligibility of reported cases including obtaining copy of signed Informed Consent Forms (ICF) for verification purposes, and de-identifying all Case Report Forms (CRFs) and supplemental documentation prior to sending to the Study Coordinating Centre for further processing and data entry.

3.4 SCIENTIFIC ADVISORY COMMITTEE

A Scientific Advisory Committee (SAC) oversees the scientific affairs of the study as needed, and is composed of experts in the fields such as neurology, teratology, epidemiology, maternal-fetal medicine, obstetrics and gynecology, pediatrics, etc. from various sectors (e.g., academia, private practice).

An individual or individuals of the experts with expertise in teratology/dysmorphology, will be a member (or members) of the SAC and function as the Birth Defect Evaluator(s) (BDE) to provide a detailed review of each reported case with a birth defect or with a condition that may potentially represent a birth defect and to reach a consensus on the classification /coding of each birth defect (see Section 9.4). The BDE is responsible for reviewing all birth defect cases received or updated during each reporting period. The BDE will report its findings to the SAC for review and approval.

The Scientific Advisory Committee does not contain any members from MAH or CRO. The Composition and details of functioning of Scientific Advisory Committee will be addressed in its Charter.

4 ABSTRACT

Title:

International LEMTRADA Pregnancy Exposure Cohort in Multiple Sclerosis

Rationale and background:

LEMTRADA is a recombinant humanized monoclonal antibody for intravenous infusion indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). LEMTRADA binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. The mechanism by which LEMTRADA exerts its therapeutic effects in MS is unknown, but may involve immunomodulation through the depletion and repopulation of lymphocytes.

There are no adequate and well-controlled studies of LEMTRADA in pregnant women. It is not known whether LEMTRADA can affect reproductive capacity or cause fetal harm when administered to a pregnant woman.

Research question and objectives:

This post authorization safety study (PASS) is an international, observational cohort study (registry) of pregnancy outcomes in women with MS exposed to LEMTRADA during pregnancy.

Pregnancy outcomes in women exposed to LEMTRADA will be compared with available data from external comparison groups: women with MS not exposed to LEMTRADA, and women without MS.

The overall goal of the registry is to compare maternal, fetal and infant outcomes in women exposed to LEMTRADA with the outcomes of unexposed external comparison groups. This registry will detect and record the following outcomes:

- Primary outcome:
  - Spontaneous abortion
- Secondary outcomes:
  - Major and minor congenital malformations;
  - Pregnancy outcome: stillbirth, elective terminations, preterm birth, full-term live birth;
  - Small for gestational age at birth;
  - Any other adverse pregnancy outcomes.

These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through the first year of life.

Study design:

This is an international, observational cohort registry of maternal, fetal and infant outcomes in women with MS exposed to LEMTRADA during pregnancy.

Pregnancy outcomes in women exposed to LEMTRADA will be compared with available data from external comparison groups: women with MS not exposed to LEMTRADA, and women without MS.

This is an observational study with no experimental intervention utilized. Women enrolled in the study may receive treatment and evaluations for their MS and their pregnancies as determined by their treating physicians in accordance with local standard of care. Information of prospective pregnancies on patient's safety and pregnancy outcome will be collected during each trimester and within 6 weeks after the end of pregnancy. For all live births, the infant's HCP will be contacted at 1 year post-delivery to obtain follow-up on the infant's health status. Information of retrospective pregnancies (exposed to LEMTRADA during pregnancy but pregnancy outcome is known at time of registry) will be collected similarly, except for information on the chronological interview during pregnancy.

The total duration of the study is expected to be approximately 5 years, with study recruitment expected to be 4 years.

Population:

Inclusion criteria:

I 01. Women with MS who were or became pregnant within the period of time between the first infusion of a course of treatment with LEMTRADA to 4 months after their last infusion for that course.

I 02. Able and willing to provide informed consent.

Exclusion criteria:

E 01. Previous enrollment in this study for a previous pregnancy.

Variables:

Rates of spontaneous abortion, major and minor congenital malformations, stillbirth, elective terminations, preterm birth, small for gestational age at birth, and any other adverse pregnancy outcomes for women exposed to LEMTRADA during pregnancy will be calculated.

These rates will be compared with corresponding rates in unexposed external comparison groups (details defined in the "Data sources" section below).

Data sources:

Exposed group:

Data of prospective pregnancies will be collected via interview during each trimester and at the pregnancy outcome interview which will occur within 6 weeks after the end of the pregnancy. Data on birth and neonatal outcomes will be collected from the women's/newborn's HCP during such pregnancy outcome interview. For all live births, the infant's HCP will be contacted at 1 year post-delivery to obtain follow-up on the infant's health status. Data will be collected on LEMTRADA exposure during pregnancy and subsequent pregnancy and fetal outcomes. Major and minor congenital malformations will be reviewed and classified by the BDE and reviewed by the SAC. This study will also collect information on maternal history including demographic information, risk factors, and medications used.

Data of retrospective pregnancies will be collected similarly except for data on the chronological interview during pregnancy as the pregnancy outcome is known at time of registry.

Comparison groups:

External comparison groups will be comprised (but not limited to) using the following sources:

- Data from the comparison groups enrolled in the North American AUBAGIO® (teriflunomide) Pregnancy Outcome Exposure Registry: an OTIS Autoimmune Disease in Pregnancy Project (Genzyme study OBS13499).
  - Cohort II (North American AUBAGIO Pregnancy Outcome Exposure Registry Cohort II) - pregnant women with MS not exposed to AUBAGIO during the current pregnancy – modified to also exclude women exposed to LEMTRADA
  - Cohort III (North American AUBAGIO Pregnancy Outcome Exposure Registry Cohort III) - pregnant women without MS and not exposed to AUBAGIO during the current pregnancy – modified to also exclude women exposed to LEMTRADA.

    NOTE: Cohort I (pregnant women with MS exposed to AUBAGIO) are excluded.
- Data from the population-based European Surveillance of Congenital Anomalies (EUROCAT) database (1).
- Data from the Metropolitan Atlanta Congenital Defects Program (MACDP) (2)

Study size:

The sample size of approximately 204 women exposed to LEMTRADA during pregnancy (prospective) is expected to achieve approximately 193 women followed up to 1 year post-delivery, allowing approximately 5% of recruited women to have missing pregnancy outcome data. With this sample size and a sample size of 117 in the comparator group, at 80% power and a 1-sided two-sample test with significance level of 0.025, we will be able to detect a 2.0-fold higher relative risk for a background spontaneous abortion rate of 13.5%, which encompasses the likely risk range for spontaneous abortions amongst women in reference cohorts. In the reference cohorts of pregnancies from women with and without MS who were not exposed to LEMTRADA, the rate of spontaneous abortion is expected to be 16.6% for women without MS (3) and 11.5% - 19.5% for women with MS) (4,5,6). Retrospective pregnancies are not part of this sample size calculation and are collected additionally.

Data analysis:

Rates and 95% confidence intervals (CI) of major and minor congenital malformations, spontaneous abortion, stillbirth, elective terminations, preterm birth, small for gestational age at birth, and any other adverse pregnancy outcomes for women exposed to LEMTRADA during pregnancy will be calculated. These rates will be compared with corresponding rates in unexposed external comparison groups (details defined in Section 4, under "Data sources") by calculating a relative risk for each outcome and its 95% CI.

For retrospectively collected pregnancies, descriptive statistics on outcomes and maternal characteristics will be provided separately from prospective cases. The retrospectively collected congenital malformation cases will also be examined to determine if there is a specific pattern of malformations observed with LEMTRADA exposure.

Milestones:

- First Patient In (start of data collection): 2015
- Study progress report: in RMP update or applicable annual report
- Last Patient In: 2018
- Last Patient Out (end of collection data): 2020
- Database lock: 2021
- Final report of study results: 2021

5 AMENDMENTS AND UPDATES

Any change to the protocol will be recorded in a written amendment, which will be signed by the Investigator/Health Care Provider and by the MAH/MAH REPRESENTATIVE. Amendment to the protocol may require regulatory submissions (e.g., Institutional Review Board [IRB]/ Independent Ethics Committee [IEC]) in accordance with local regulations. Submission package will include two documents: approved amended protocol and approved amendment (i.e., a summary of changes to the protocol).

In some cases, an amendment may require a change to the informed consent form (ICF).

6 MILESTONES

Milestone	Planned date
First Patient In (Start of data collection)	2015
Study Progress Report	In RMP update or applicable annual report
Last Patient In	2018
Last Patient Out (end of data collection)	2020
Database lock	2021
Final report of study results	2021

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

LEMTRADA is a recombinant humanized monoclonal antibody for intravenous infusion indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS). LEMTRADA binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. The mechanism by which LEMTRADA exerts its therapeutic effects in MS is unknown, but may involve immunomodulation through the depletion and repopulation of lymphocytes.

There are no adequate and well-controlled studies of LEMTRADA in pregnant women. It is not known whether LEMTRADA can affect reproductive capacity or cause fetal harm when administered to a pregnant woman. The effects of LEMTRADA on fertility and reproductive performance have been evaluated in the human CD52 (huCD52) transgenic mouse. In female mice, doses of 10 mg/kg/day of LEMTRADA administered for 5 days prior to cohabitation reduced gestational weight gain relative to the vehicle controls. Furthermore, Caesarean-sectioning and litter observations showed that the average number of corpora lutea and implantation sites per mouse were reduced following doses of 10 mg/kg/day for 5 days. Administration of 3 or 10 mg/kg LEMTRADA for 5 days in the huCD52 transgenic mouse during the period of fetal organogenesis (Gestation Day [GD] 6 through 10, or GD 11 through 15) resulted in no overt signs of maternal toxicity and, importantly, produced no gross external, soft tissue, or skeletal fetal effects. However, significant increases in the number of dams with all conceptuses dead or resorbed, along with a concomitant reduction in the number of dams with viable fetuses occurred in animals exposed to 10 mg/kg/day LEMTRADA during GD 11 through 15. The fetal loss was believed to be maternally mediated, as complete (or near complete) litter loss was only observed in a few dams, whereas an effect mediated by fetal response would likely result in numerous dams having lost a portion of their pups since the breeding strategy was such that not all pups expressed the huCD52 transgene. Exposure to LEMTRADA during presumed gestation and lactation resulted in alterations in total lymphocyte numbers and subpopulations during each of the periods of immune development evaluated. When dosed at 10 mg/kg/day for five days during lactation, LEMTRADA had no effect on the cognitive, physical, and sexual development of pups.

In the huCD52 transgenic mouse, there is evidence that during pregnancy, and as pregnancy proceeds, the effect of a changing body composition leads to changes in LEMTRADA pharmacokinetics. This is characterized by faster clearance and a concomitant diminishing of overall LEMTRADA exposure. This is likely a result of placental transfer to the fetus, since LEMTRADA was detected in mice fetuses exposed to LEMTRADA during gestation. Also, human immunoglobulin G (IgG) is known to cross the placental barrier, and therefore, LEMTRADA may cross the placental barrier and potentially cause fetal B and T lymphocyte depletion. The relevance of the observed effects of LEMTRADA in nonclinical studies to humans is uncertain.

There were a significant number of pregnancies during clinical trials with LEMTRADA in multiple sclerosis. A total of 140 pregnancies in 101 alemtuzumab-treated patients have been reported in the MS clinical program as of 04 October 2013.

Through 04 October 2013, there was one report of a major congenital malformation in the fetus or neonate of a 38 year old woman exposed to LEMTRADA in a Genzyme clinical study. In that case, pregnancy occurred 21 months after receiving the 2nd Lemtrada treatment course, and an elective abortion was performed when ultrasound during 14th gestational week showed fetal defects of cystic hygroma and hypoplastic heart. Cystic hygroma associated with other congenital anomalies (e.g., cardiac) are generally due to chromosomal abnormalities, the risk of which may increase with advancing maternal age. No other major congenital abnormalities or birth defects have been reported through 04 October 2013 for pregnancies in women exposed to LEMTRADA in the MS clinical development program.

The majority of individuals who are diagnosed with MS are women of childbearing age (7). The higher prevalence of MS in women during their reproductive years reinforces the importance of understanding disease impact and treatment safety during pregnancy. Although MS itself is not known to be a risk to fertility or the outcome of pregnancies, the use of immunomodulatory and immunosuppressive drugs to treat the disease may have an impact on pregnancy outcome. This observational cohort study will monitor pregnancies in women exposed to LEMTRADA to evaluate their pregnancy outcomes.

7.2 RATIONALE

Given the prevalence of MS in women of childbearing age, a greater overall number of exposed pregnancies can be expected following regulatory approval and market penetration. It is not known if LEMTRADA could harm an unborn child. Therefore, the lack of sufficient human fetal safety data for LEMTRADA makes pregnancy outcome monitoring an important component of research on the safety of LEMTRADA.

The proposed registry utilizes an international, observational cohort design to evaluate rates of adverse pregnancy outcomes in women exposed to LEMTRADA during pregnancy. These rates will be compared with corresponding rates in unexposed external comparison groups (details defined in Section 4, under “Data sources”) to assess if the risk of any observed adverse pregnancy outcomes in women exposed to LEMTRADA exceeds rates observed in unexposed external comparison groups. Women exposed to LEMTRADA during pregnancy are eligible to enroll provided their pregnancy is ongoing. Women with early prenatal testing are permitted into the study; statistical analysis will be adapted to detect potential impact of prenatal testing on the pregnancy outcomes.

Pharmacokinetic data on LEMTRADA suggests that LEMTRADA plasma concentrations become undetectable at 1 month post-treatment but effective contraceptive use is the primary recommendation when receiving a course of treatment with LEMTRADA and for 4 months following that course of treatment (a period >5 half-lives). Therefore, exposure inclusion criteria for this study dictate that participants in this registry are eligible if they were or become pregnant at any time from initiation of a course of treatment with LEMTRADA through the 4 months period following their last LEMTRADA infusion for that course of treatment.

8 RESEARCH QUESTION AND OBJECTIVES

This PASS is an international, observational cohort study (registry) of pregnancy outcomes in women with MS exposed to LEMTRADA during pregnancy.

Pregnancy outcomes in women exposed to LEMTRADA will be compared with available data from external comparison groups: women with MS not exposed to LEMTRADA, and women without MS.

The overall goal of the registry is to compare maternal, fetal and infant outcomes in women exposed to LEMTRADA with the outcomes in women from unexposed external comparison groups during pregnancy and to assess if the risks of any adverse pregnancy outcomes and birth defects in women exposed to LEMTRADA during pregnancy exceeds the risks in women of unexposed external comparison groups. The registry will detect and record the following outcomes:

- Primary outcome:
  - Spontaneous abortion
- Secondary outcomes:
  - Major and minor congenital malformations;
  - Pregnancy outcome: stillbirth, elective terminations, preterm birth, full-term live birth;
  - Small for gestational age at birth;
  - Any other adverse pregnancy outcomes.

These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through the first year of life.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This post authorization safety study (PASS) is an international, observational cohort (registry) of pregnancy outcomes in women with MS exposed to LEMTRADA during pregnancy.

Pregnancy outcomes in women exposed to LEMTRADA will be compared with available data from external comparison groups: women with MS not exposed to LEMTRADA, and women without MS (details defined in Section 4, under "Data source").

This is an observational study with no experimental intervention utilized. Women enrolled in the study may receive treatment and evaluations for their MS and their pregnancies as determined by their treating physicians in accordance with local standard of care. Information of prospective pregnancies on patient's safety and pregnancy outcome will be collected during each trimester and within 6 weeks after the end of pregnancy. For all live births, the infant's HCP will be contacted at 1 year post delivery to obtain follow-up on the infant's health status. Information of retrospective pregnancies (exposed to LEMTRADA during pregnancy but pregnancy outcome is known at time of registry) will be collected similarly except for information on the chronological interview during pregnancy.

Women who were pregnant or became pregnant within the period of time between their initiating a course of treatment with LEMTRADA to 4 months after their last infusion for that course may be enrolled, provided their pregnancy is ongoing.

A total of approximately 204 women exposed to LEMTRADA during pregnancy (prospective) will be enrolled to achieve approximately 193 women followed up to 1 year post-delivery. Retrospective pregnancies are not part of this sample size calculation and are collected additionally.

Women exposed to LEMTRADA during pregnancy will be recruited from a variety of sources, including referral of female patients who become pregnant while enrolled in a separate observational study; referral of LEMTRADA-exposed female patients reporting pregnancies identified through routine pharmacovigilance activities, and LEMTRADA-exposed female patients reporting pregnancies identified through study outreach activities such as study postings on applicable websites. Enrollment as early in the pregnancy as possible is encouraged. Study enrollment is voluntary and requires informed consent in accordance with local requirements.

Information will be collected from applicable HCPs of the enrolled women. For enrolled women, data will be collected by National Coordinator via interview with women during each trimester and within 6 weeks after the completion of the pregnancy. Data on birth and neonatal outcomes will also be collected from the women's HCP within 6 weeks of pregnancy completion. For all live births, the infant's HCP will be contacted at 1 year post-delivery to obtain follow-up on the infant's health status.

Data will be collected on LEMTRADA exposure during pregnancy and subsequent pregnancy and fetal outcomes. Major structural malformations identified in the perinatal period through 12 months of life will be collected and classified. This study will also collect information on maternal history including demographic information, risk factors, and medications used.

9.2 SETTING

The registry will enroll pregnant women with MS who have had any pregnancy exposure to LEMTRADA from North America (NA), Europe (EU) and the rest of the world (ROW).

To maximize enrollment, this study employs an open enrollment approach. Any eligible woman, receiving health care in a country in which this study is operating, is encouraged to participate through her HCP(s) and the National Coordinator. The pregnant participant is followed until the end of pregnancy. If the outcome of pregnancy is a live born infant, the infant outcome, including effects on postnatal growth and development, will be assessed through the first year of life. Maternal enrollment and follow-up data may be reported by any of the woman's HCPs (e.g., obstetrician, neurologist, general/family physician, genetic counselor). Infant follow-up is provided by the infant's HCP whose expertise is typically in pediatrics or family medicine.

There is no forced selection process for patients or physician reporters in this protocol; therefore, prospectively enrolled women are expected to be representative of the source population in the respective countries.

9.2.1 Duration of the study

The total duration of the study is from the time the first woman exposed to LEMTRADA during pregnancy enrolls to when all enrolled women are followed up to 1 year post-delivery. The full study duration is expected to be approximately 5 years.

9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

A woman is eligible for the study if all of the following apply:

I 01. Women with MS who were or became pregnant within the period of time between the first infusion of a course of treatment with LEMTRADA to 4 months after their last infusion for that course.

I 02. Able and willing to provide informed consent for study participation and the requirement of the study. Informed consent will be obtained at the time of enrollment in accordance with local regulatory requirements.

9.2.2.2 Exclusion criteria

E 01. Previous enrollment in this study for a previous pregnancy.

9.2.3 Analysis population(s)

The primary analysis population will include all women (prospectively) enrolled in the study who meet the study inclusion criteria and have pregnancy outcome data recorded. Outcomes for the primary analysis population will primarily be compared with pregnancy outcomes in unexposed external comparison groups.

Ascertainment of pregnancy outcomes will be considered completed when:

- Pregnancy outcome is known and was not a live birth, or
- Pregnancy outcome was a live birth and the 1-year post-delivery follow-up has been completed, or
- The woman has been classified as lost to follow-up, or
- The woman has withdrawn informed consent prior to ascertainment of pregnancy outcome.

Otherwise; the pregnancy outcome will be considered as pending.

For the analysis, descriptive analyses of baseline characteristics of the additional populations of all enrolled women (including women whose pregnancy outcome data are unknown, such as lost to follow up), and the subset of women whose pregnancy outcome data are unknown, will also be calculated.

Retrospective pregnancy population will provide qualitative data which will be descriptively analyzed independent of the prospectively collected primary analysis population.

9.2.4 Modalities of recruitment

9.2.4.1 Investigator's selection

All awareness activities will be targeted to HCPs, including neurologists, in participating countries. MAH/MAH representative will attempt to raise awareness and encourage reporting by posting contact information: 1) on the study website; 2) in notices or publications in appropriate journals targeted to HCPs; 3) other websites as appropriate; 4) exhibits at clinical meetings. Other awareness avenues will be explored and utilized.

The study website previews to include general information regarding the study design, National Coordinators' contact information, enrollment eligibility and participation, instructions, patient informed consent forms, medical release forms.

To maximize enrollment, the registry employs an open enrollment approach. All enrollment and follow-up activities within a specific country are overseen by the country-specific National Coordinator. Multiple HCPs may be asked to report on an individual patient to the National Coordinator. It is anticipated that the reporters will be physicians or other HCPs with expertise in neurology, internal medicine, obstetrics, midwifery, pediatrics, family medicine, or genetic counseling.

Patients in other observational studies identified as having exposure to LEMTRADA during pregnancy will be referred for potential enrollment into this registry for targeted follow-up and standardized analysis.

9.2.4.2 Patient selection

Women exposed to LEMTRADA during pregnancy will be recruited over a period of approximately 4 years from a variety of sources, including:

- Referral of female patients who become pregnant while enrolled in a separate international or local observational study Referral of LEMTRADA-exposed female patients reporting pregnancies identified through routine pharmacovigilance activities.
- LEMTRADA-exposed female patients reporting pregnancies identified through various outreach activities. For example, in some regions prescribing information and patient labelling may reference the pregnancy registry. Additional outreach strategies will include dissemination of information about the study and how to enrol through a variety of venues. Outreach materials for the study will direct HCPs and patients to the pregnancy cohort Study Coordinating Centre phone line and websites.

Study enrolment is voluntary and requires informed consent in accordance with local requirements. HCP, taking care of an eligible woman will explain the study protocol and eligibility criteria to women who contact or will be referred to them. A National Coordinator will be informed of a potentially eligible woman by such HCP. National Coordinator will instruct the HCP on obtaining informed consent and on collecting further data for this study. Women who meet the eligibility criteria and are interested in participating will be administered informed consent by HCP prior to conducting the first maternal interview. Informed consent including compliance with locally applicable data privacy legislation (e.g., in Europe, compliance with Directive 95/46/EC) will be obtained in accordance with local regulatory requirements. If applicable and where directed by local requirements, informed consent of fathers will also be obtained.

All eligible women who agree to participate and provide informed consent while the study enrolment period is open will be able to participate in the study. Information from women exposed to LEMTRADA during pregnancy who do not meet study eligibility criteria or decline participation will be handled as a separate pregnancy reports and referred to the MAH/MAH representative.

Variables: Rates of spontaneous abortion, major and minor congenital malformations, stillbirth, elective terminations, preterm birth, small for gestational age at birth, and any other adverse pregnancy outcomes for women exposed to LEMTRADA during pregnancy will be calculated. These rates will be compared with corresponding rates in unexposed external comparison groups (details defined in the Section 9.3).

9.3 DATA SOURCES

Exposed group:

For enrolled women (prospective pregnancies), data will be collected via interview during each trimester and at the pregnancy outcome interview which will occur within 6 weeks after the end of the pregnancy. Data on birth and neonatal outcomes will be collected from the women's/newborn's HCP during such pregnancy outcome interview. For all live births, the infant's HCP will be contacted at 1 year post-delivery to obtain follow-up on the infant's health status. Data will be collected on LEMTRADA exposure during pregnancy and subsequent pregnancy and fetal outcomes. All variables defined in this protocol (Section 8, primary and secondary outcomes) will be collected and classified. This study will also collect information on maternal history including demographic information, risk factors, and medications used. Information of retrospective pregnancies will be collected similarly except for information on the chronological interview during pregnancy, as pregnancy outcome is known at time of registry.

Comparison groups:

External comparison groups will be comprised (but not limited to) using the following sources:

- Data from the comparison groups enrolled in the AUBAGIO® (teriflunomide) North American registry "Teriflunomide Pregnancy Outcome Exposure Registry: an OTIS Autoimmune Disease in Pregnancy Project" (Genzyme study OBS13499):
  - Cohort II - (North American AUBAGIO Pregnancy Outcome Exposure Registry Cohort II) - pregnant women with MS not exposed to AUBAGIO during the current pregnancy – modified to also exclude women exposed to LEMTRADA
  - Cohort III - (North American AUBAGIO Pregnancy Outcome Exposure Registry Cohort III) - pregnant women without MS and not exposed to AUBAGIO during the current pregnancy – modified to also exclude women exposed to LEMTRADA

  NOTE: Cohort I (pregnant women with MS exposed to AUBAGIO) are excluded
- Data from the population- based European Surveillance of Congenital Anomalies (EUROCAT) database (1).
- Data from the Metropolitan Atlanta Congenital Defects Program (MACDP) (2)

9.4 BIRTH DEFECT EVALUATION

If a birth defect is reported, the entire case is initially reviewed by the registry's Birth Defect Evaluator (BDE), an individual or individuals with expertise in teratology/dysmorphology. Following the BDE's review, the case is presented to the Scientific Advisory Committee (Section 3.4) for review and approval.

The BDE is charged with reviewing all details of the case and:

- Requesting further information as targeted follow-up, if needed;
- Coding each reported birth defect in accordance with the coding methodology used for Cohort II/III from the AUBAGIO registry;
- Identifying and documenting potential confounders, if available;
- Writing a brief narrative summarizing the review;
- Presenting the case to the Scientific Advisory Committee for further review and consensus.

For all reports of birth defects, the birth defect review process is conducted on birth defect status of each individual outcome. Therefore, a HCP may present a case as a birth defect, but after the BDE's review and coding, the registry may modify the final coding as "not a defect".

9.5 STUDY SIZE

9.5.1 Determination of sample size (LEMTRADA exposed)

The sample size of approximately 204 women exposed to LEMTRADA during pregnancy (prospective) is expected to achieve approximately 193 women followed up to 1 year post-delivery, allowing approximately 5% of recruited women to have missing pregnancy outcome data. With this sample size and a sample size of 117 in the comparator group, at 80% power and a 1-sided two-sample test with significance level of 0.025, we will be able to detect a 2.0-fold higher relative risk for a background spontaneous abortion rate of 13.5%, which encompasses the likely risk range for spontaneous abortions amongst women in the reference cohorts. In the reference cohorts of pregnancies from women with and without MS who were not exposed to LEMTRADA, where the rates of spontaneous abortion is expected to be 16.6% for women without MS (3) and 11.5% - 19.5% for women with MS (4,5,6). Retrospective pregnancies are not part of this sample size calculation and are collected additionally.

Table 1 shows the type of differences that may be detected comparing LEMTRADA-exposed pregnancies with various background rates for spontaneous abortion and any birth defects. For purposes of sample size calculation, a combination of general population background rates and rates published in the literature for women with MS with pregnancies unexposed to disease-modifying therapy were used.

Table 1 - Sample Size and Detectable Effect Size for Selected Endpoints

Endpoint	Population	Background Rate	Total Sample size	RR
Spontaneous abortion	General population	16.6% (3)	204 (Effective 193)	1.86
	Women with MS	11.5% (5)	204 (Effective 193)	2.12
	Women with MS	19.5% (4)	204 (Effective 193)	1.77
	Background Comparator Groups	13.5%	204 (Effective 193)	2.0
Any major birth defect	General population	3% (8,9)	204 (effective 154)	4.05
	Women with MS	3% (10)	204 (effective 154)	4.05

RR: Relative Risk.

Sample size calculations were performed using EAST software version 6.2.

Assuming 5% drop out (outcome unavailable): 204*95%=193 patients will permit detection of RR=2.0 for a background rate of 13.5% with 80% power and 0.025 significance level based on 1-sided two sample Fisher's exact test (with comparator group sample size =117)

Assuming 80% live birth, 193*80%=154 live births.

References: In the MS treated women, the data from interferon B1A treated pregnant women showed discrepancy between the initial observation from a limited number of pregnancies from the clinical program and data collected in post-marketing setting. The rate of spontaneous abortions was 19.5% (8/41) from the clinical program (4), 11.5% (49/425) from prospective cases of PV databases (5), and 12.4% (28/226) from the pregnancy exposure registry (6).

9.5.2 Sample size of external comparison groups (LEMTRADA non-exposed)

Sample size is set at 125 in comparison Cohorts II and III respectively in "AUBAGIO (teriflunomide) Pregnancy Outcome Exposure Registry: an OTIS Autoimmune Disease in Pregnancy Project" (Genzyme study OBS13499)." For the sample size calculation above, it is assumed that a sample size of 125 in the comparator group includes 4% missing data and 2% were exposed to LEMTRADA (in Cohort II), resulting in 125*96%*98% = 117 subjects.

9.6 DATA MANAGEMENT

9.6.1 Data collection schedule

Table 2 - study data collection schedule

Data collected/ Evaluation	Enrolment Interview (ideally <13 weeks' gestation)	2nd Trimester Interview (16-20 weeks' gestation) *a*	3rd Trimester Interview (26-32 weeks' gestation) *a*	Pregnancy Outcome Interview (within 6 weeks after the end of the pregnancy) *a b*	Infant Status Update (1 year after delivery) *b*	Targeted Follow-up (after BDE review *c*	Retrospective Pregnancy (pregnancy outcome known at time of enrollment)
Enrollment and Informed Consent	X						X
Contact Information and Demographics	X						X
Targeted Medical History	X					X	X
Pregnancy History	X						X
Risk Factors *d*	X	X	X			X	X
LEMTRADA Exposure History *e*	X						X
Concomitant Medications *f*	X	X	X	X			X
Pregnancy Status/Outcome		X	X	X		X	X
Foetal/Pediatric Outcomes				X	X	X	X
Medical Record Review of Pregnancy Outcome				X		X	X
HCP Questionnaire on Infant Status at 1 Year					X *g*		X
Collection of selected adverse events *h*	X	X	X	X	X	X	X

a The interview can be conducted by phone or in person. Whenever medical documentation is needed (summary from maternity, other hospitalization or investigation summaries, etc.), – they can be collected by electronic transfer

b Active contact by national Coordinator, if needed, not later, than 6 weeks after expected delivery date and 1 year after delivery for live birth

c Obtain this information if information is requested following Birth Defect Evaluator review

d Risk factors: Smoking, alcohol use, illicit drug use, pre-pregnancy body mass index (BMI), etc.…

e Exposure history for current pregnancy only

f All medications for MS from the onset, also – other medications relevant to the disease or ongoing within 1 month to inclusion

g For live-birth outcomes only, if woman has not withdrawn consent

h AEs to be reported include: a) all serious adverse events, including medically important events and pregnancy outcome related events such as all major and minor malformations, spontaneous abortions, stillbirths, elective terminations, neonatal deaths ,preterm birth, small for gestational age at birth, and any other adverse pregnancy outcomes occurring in a LEMTRADA-exposed pregnancy; b) non serious AEs, which to the opinion of HCP or National Coordinator may potentially have impact on the outcome of the pregnancy, whether causally related to the drug product or not.

NOTE: BDE=Birth Defect Evaluator

9.6.2 Data collected

9.6.2.1 Date collected from the mother (patient) by Health Care Provider (HCP)

Once patients sign the informed consent, patients' enrollment and follow up information are collected by the HCP. Whenever permitted in local legislation, signature of ICF will mean that the pregnant patient consents that medical records of herself and of the infant can be released by the HCP to the NC for further use in this Registry. After the ICF is signed, the enrolment interview can be done by HCP or registry staff if the HCP is not available; follow-up interviews can be done by phone or in person (by HCP or registry staff). Forms with patients' data completed by the HCP are sent to the National Coordinator by mail, fax, or email (on a secure server). Upon receipt, the National Coordinator reviews the forms for completeness, queries the HCP for missing data, and de-identifies and key-codes all forms before entering them into the CRF. Information to be collected during maternal interviews includes:

- Demographics: maternal age, maternal race/ethnicity (as per local regulations), education, family income category.

  Of note: Patient race or ethnicity (e.g., "Caucasian/White, Black, Asian/Oriental, Others" will be collected in this study because these data are required by several regulatory authorities (e.g., on afro American population for Food and Drug Administration (FDA), on Japanese population for the PMDA in Japan, or on Chinese population for the CFDA in China)"
- Targeted medical history including prior treatment for MS.
- History of previous pregnancies and outcomes of each:
  - Pregnancy outcome: live birth, stillbirth, spontaneous abortion, induced abortion,
  - Pregnancy complications,
  - Fetal/neonatal abnormalities and type.
- Current pregnancy: fertility treatments (if applicable), date of last menstrual period, expected delivery date, prenatal tests conducted and results, pregnancy status.
- Risk factors: Smoking, alcohol use, illicit drug use, pre-pregnancy BMI
- LEMTRADA exposure (infusion dates).
- Concomitant medications including over-the-counter and prescription medications, vitamin supplements including folic acid, herbal medicines from one month prior to the date of enrollment.
- At pregnancy completion (as applicable depending on pregnancy outcome)
  - Pregnancy outcome (live birth, spontaneous abortion, stillbirth, induced abortion) and type (singleton or multiple),
  - For live births.

a) Gender, gestational age at delivery, mode of delivery, type/length of hospital stay, maternal and neonatal complications, maternal weight gain, presence or absence of major and minor structural defects, Apgar scores, birth weight, birth length, and head circumference.

- For other outcomes.

a) Gestational age at time of event, pathology results if available, and presence or absence of major and minor structural defects. For stillborn infants - gender, birth size, and autopsy results.

- Safety data
  - All SAEs including medically important events (see Section 11.1.1 for details),
  - All non-serious adverse events which per opinion of HCP/National Coordinator potentially have an impact on pregnancy outcomes.

At the conclusion of the pregnancy outcome interview, upon local practice, when local legislation requires this in addition to ICF signature, women can be mailed a packet with medical records release forms (or equivalent) from the pre- and postnatal HCP, the delivery hospital, and the pediatrician. Women will be asked to sign the medical records release forms and return the signed forms to the HCP(s). This process is to allow the National Coordinator to contact HCPs to confirm pregnancy outcomes and other above described data.

For retrospective cases, all data collections described above are applicable except that there would be no trimester interviews because the pregnancy outcome is already known.

Targeted follow-up

If a birth defect is noted, additional details regarding the birth defect may be requested from HCP by NC or by BDE to further define the etiology, facilitate classification, and to assess the presence of potential confounders of the birth defects. In addition, any specific questions the BDE (see Section 9.4) might have following initial review of the case will be included on the Targeted Follow-up Form.

The Targeted Follow-up Form collects the following from the reporter of the birth defect(s) or other appropriate HCP:

- Additional details of the birth defect (from initial report)
  - Assessment of etiology from HCP perspective
  - Requirement of surgical intervention to treat the birth defect (if so, dates and details)
- Potentially contributory factors
  - Medications or other products or agents taken during pregnancy
  - Maternal and paternal occupation
  - Concurrent medical/clinical conditions (occurring prior to and/or during pregnancy)
  - Any other factors that might have contributed to this outcome

- Specific targeted questions requested by the Birth Defect Evaluator reviewing the case relevant to this birth defect/outcome of interest
- Additional comments addressing factors that may have had an impact on the pregnancy outcome, birth defect, or other outcome of interest.

9.6.2.2 Data collected from Health Care provider (HCP) by National Coordinator

All data collected by HCP will be submitted to respective National Coordinator.

National Coordinator will review the medical records provided by HCPs and will contact HCPs, whenever needed, will complete collection of data with queries and clarifications, in order to confirm pregnancy outcomes - by telephone, faxed/mailed forms or email.

For live birth outcomes, infant HCPs will be contacted 1 year post-delivery to complete a standard questionnaire containing information on infant size, postnatal complications, congenital anomalies, method of infant feeding, and targeted infant medical history (e.g., neonatal Grave's disease, recurring or serious infections, autoimmune disorders).

Information to be verified by HCPs includes:

- Pregnancy outcome (live birth, spontaneous abortion, stillbirth, induced abortion) and type (singleton or multiple).
- For live births
  - Gender, gestational age at delivery, mode of delivery, type/length of hospital stay, maternal and neonatal complications, maternal weight gain, presence or absence of major and minor structural defects, Apgar scores, birth weight, birth length, and head circumference.
- For other outcomes
  - Gestational age at time of event, pathology results if available, and presence or absence of major and minor structural defects. For stillborn infants - gender, birth size, and autopsy results.

9.6.3 Site/Investigators questionnaire

Not applicable.

9.6.4 Patient/Subject tracking log (if applicable)

Not applicable.

9.6.5 Procedure for withdrawal of patients from study follow-up schedule

The HCPs and National Coordinators will endeavor to conduct follow-up in accordance with the protocol's study data collection schedule for all women enrolled in the study who are eligible, have provided informed consent, and have completed the initial enrolment interview. National Coordinator will make multiple attempts to contact patients via HCPs with valid contact information using multiple mechanisms (e.g., phone, fax, mail) before a woman is considered lost to follow-up. Women with missing pregnancy outcome information due to lost to follow-up will be described in study enrollment-related analyses but will be excluded from the denominator of outcome-related analyses.

Participation in the study is voluntary and women may withdraw consent to participate in follow-up visits at any time. For women who withdraw consent, study participation for both the woman and her infant will terminate immediately upon her request. Once a woman is withdrawn from the study, routine pharmacovigilance follow-up procedures will be applied for all ongoing adverse events.

9.7 DATA ANALYSIS

9.7.1 Primary analysis

The primary analysis population will include all women enrolled in the study prospectively who meet the study inclusion criteria and have pregnancy outcome data recorded. Outcomes for the primary analysis population will primarily be compared with pregnancy outcomes in unexposed external comparison groups. Ascertainment of pregnancy outcomes will be considered completed when:

- Pregnancy outcome is known and was not a live birth, or
- Pregnancy outcome was a live birth and the 1-year post-delivery follow-up has been completed, or
- The woman has been classified as lost to follow-up, or
- The woman has withdrawn informed consent prior to ascertainment of pregnancy outcome.

Otherwise, the pregnancy outcome will be considered as pending.

9.7.2 Secondary analysis

For the final analysis, descriptive analyses of baseline characteristics of the population of all prospectively enrolled women (including women whose pregnancy outcome data are unknown, such as lost to follow up), and the subset of women whose pregnancy outcome data are unknown, will also be calculated. Additional descriptive analyses will be provided on patient characteristics for the retrospectively collected pregnancies separately.

9.7.3 Interim analysis

Not applicable.

9.7.4 Analysis variables

Definitions of pregnancy outcomes are consistent with, but not limited to, definitions used by the Center for Disease Control and Prevention Metropolitan Atlanta Congenital Defects Program (CDC MACDP), the National Center for Health Statistics (NCHS), and Organization of Teratology Information Specialists (OTIS) (2,11). Overall pregnancy outcome will be classified into one of the following mutually exclusive categories: spontaneous abortions, induced abortions/elective terminations, stillbirth, preterm birth and live birth. Every birth defect identified in a live birth will be classified into major or minor congenital malformation.

Other outcomes of interest are: minor congenital malformations, preterm birth, small for gestational age at birth, and any other adverse pregnancy outcomes. The study will endeavor to assess all pregnancy outcomes for the presence of malformations and functional deficit in the infant up to 1 year of age. A detailed description of pregnancy outcomes is provided in Appendix A.

Additional analysis variables such as maternal age, smoking status during pregnancy, and maternal comorbidities may be included in analyses as important confounders or in subgroup analyses. These additional variables will be fully described in a separate statistical analysis plan which will be developed and finalized prior to database lock.

9.7.4.1 Main criteria

Main criterion is rate of spontaneous abortion in the prospectively collected LEMTRADA-exposed group versus comparison cohorts of pregnancies from women with and without MS who were not exposed to LEMTRADA. Descriptive statistics of maternal and pregnancy characteristics and the timing of exposure will be provided for retrospectively collected cases of spontaneous abortions to qualitatively describe this patient population.

9.7.4.2 Other criteria

Other criteria are rates of major and minor malformations will be classified according to the MACDP (2) for women exposed to LEMTRADA during pregnancy ascertained through the first year of life of the infant. The rates of the prospectively collected cases will be compared with corresponding rates in unexposed external comparison groups. Descriptive statistics of maternal and pregnancy characteristics as well as the timing of LEMTRADA exposure will be provided for retrospectively collected cases of congenital malformations. These retrospectively collected cases will also be examined (by the birth defect evaluator) to determine if there is a specific pattern of malformations observed with LEMTRADA exposure.

Additionally, pregnancy outcomes (stillbirth, elective terminations, preterm birth), small for gestational age at birth, and any other adverse pregnancy outcomes for women exposed to LEMTRADA during pregnancy are included. Malformations will be classified according to the MACDP (2). These rates of the prospectively collected cases will be compared with corresponding rates in unexposed external comparison groups. Maternal and pregnancy characteristics, as well as the timing of exposure, will be described qualitatively for retrospectively collected cases of the other pregnancy outcomes.

9.7.4.3 Criteria obtained from comparison cohorts

The following comparison groups in the AUBAGIO® (teriflunomide) North American pregnancy exposure registry (Genzyme study OBS13499) will be used:

- Cohort II - (North American AUBAGIO Pregnancy Outcome Exposure Registry Cohort II) -pregnant women with MS not exposed to AUBAGIO during the current pregnancy – modified to also exclude women exposed to LEMTRADA
- Cohort III – (North American AUBAGIO Pregnancy Outcome Exposure Registry Cohort III) - pregnant women without MS and not exposed to AUBAGIO during the current pregnancy – modified to also exclude women exposed to LEMTRADA

  NOTE: Cohort I (pregnant women with MS exposed to AUBAGIO) are excluded

Patient-level data from the AUBAGIO pregnancy registry are made available to the sponsor (Genzyme, a Sanofi Company) when data has been stripped of personal identifiers.

Following variables will be collected:

- Maternal age
- Maternal race/ethnicity
- Socioeconomic status
- Prior pregnancy history: gravidity/parity and previous outcomes
- Periconceptional use of folic acid containing supplements
- Unintended pregnancy
- Gestational age at enrollment
- Exposure to other medications (including known teratogens) and other MS medications
- Comorbidities
- Disease severity measure(s)

9.7.5 Statistical methods

Endpoints are prospectively collected rates of spontaneous abortion, major and minor congenital malformations, stillbirth, elective terminations, preterm birth, small for gestational age at birth, and any other adverse pregnancy outcomes for women exposed to LEMTRADA during pregnancy.

All the comparisons below between women exposed to LEMTRADA during pregnancy (prospectively collected) and unexposed comparison groups will be carried out separately against each comparison group.

Rates and 95% CI will be calculated. Rates will be compared between women exposed to LEMTRADA during pregnancy (prospective) and women in unexposed comparison groups by calculating the relative risk (RR) and its 95% CIs. As the majority of the events rates are anticipated to be low, when applicable, comparisons will be conducted using exact statistical methods.

A supportive analysis of (prospective) spontaneous abortion as a time-to-event endpoint will be conducted using the Kaplan-Meier method adjusting for left-truncation. If data are available, propensity score matching and covariate adjustment may be used in the Cox regression context with left-truncation to adjust for potential confounding factors, such as gestational age at enrollment, comorbidities, prior birth defects/abnormalities, exposure to other medications, etc.

For other endpoints (prospective), if data are available, propensity score matching and covariate adjustment may also be used in the logistic regression context to adjust for potential confounding factors. These approaches will reduce the influence of risk modifiers in determining the event risk ratio between Lemtrada-exposed women and non-Lemtrada-exposed women.

Qualitative descriptive statistics on maternal and pregnancy characteristics and the timing of LEMTRADA exposure will be provided for the retrospectively collected pregnancy cases.

Additional supportive analyses will be documented in the statistical analysis plan (SAP).

9.8 QUALITY CONTROL

9.8.1 Data collection, validation and data quality control at MAH representative level

Data will be collected by the HCPs, providing care to the woman and/or infant, as applicable. Data recorded from interviews or abstracted from medical records are considered the primary data sources for this study and will be retained and reported to National Coordinator by the HCP. Subsequently data will be entered into a study-specific database and maintained by National Coordinator. All data entry will be reviewed for logical errors by the National Coordinator. Subsequent review of data will be done by CRO's staff (e.g., study data manager) and 100% of key variables will be double-checked for accuracy of data entry. The study statistician of MAH/MAH representative will also conduct reviews of the cumulative data from the study database for distributions and values that are illogical.

Access to the database will be controlled by password, with different access privileges assigned to the data entry staff and administrative staff. These privileges will be outlined in detail in relevant operational documents. An audit log is built into the database to archive all such entry edits. Hard copies of patient files and signed informed consent forms will be kept in a locked cabinet by National Coordinator/involved HCP as appropriate.

Additional details regarding data collection and validation procedures will be detailed in appropriate operational documents

9.8.2 Data quality control at site level

Pregnancy outcomes reported by women enrolled in the study will be verified by HCPs responsible for the care of enrolled women and their infants through medical record review.

The methodology of data Quality Control and appropriate consecutive corrective actions will be detailed in the study manual.

9.9 LIMITATIONS OF THE RESEARCH METHODS

As reporting of pregnancies is totally voluntary, it is possible that even in prospectively reported cases, potential bias could exist.

The primary limitation of an international, prospective observational cohort study is selection bias (12). Women who voluntarily enroll may represent particularly high or low risk pregnancies, leading to potential over- or under-ascertainment of potential malformations and adverse pregnancy outcomes such as spontaneous abortion. The impact of selection bias can be minimized through robust outreach to recruit women exposed to LEMTRADA during their pregnancy, and efforts to retain all women who enroll into the study through the entire study follow-up period. Outreach strategies will include dissemination of information about the study and how to enroll through a variety of venues. Another potential limitation is that the calculation of fetal malformations will exclude information from spontaneous abortions, induced abortions, or fetal deaths where information on malformations was not available. For these excluded fetal losses, it is unknown what percentage would have resulted in potentially normal outcomes or malformations, leading to potential over or underestimation of malformation rates. The use of unexposed external comparison groups will also address these limitations to some extent.

Pregnancy outcome information is considered “lost to follow-up” if unobtainable after 4 attempts. It is possible that outcomes among pregnancies lost to follow-up could differ from those with documented outcomes. Because of differences in follow-up procedures across countries and individual reporting patterns, it is currently not possible to assess with any certainty what impact the potential biases the losses to follow-up may have on the analysis. However, efforts at comparing some of the characteristics of each group may be conducted in an attempt to address this potential source of bias.

The protocol also recognizes that some defects and other infant abnormalities may not be evident at birth and are often diagnosed during the first year of life. In this study, the infant is followed until one year of age. Requiring the Primary Analysis Population to have complete follow-up until one year of age raises the potential for lost to follow-up. Lost to follow-up must be minimized in this study, in particular, because pregnancy exposures are expected to be rare and accordingly, enrollment is expected to be difficult. A subgroup analysis will be conducted to estimate the rate of birth defects among infants with complete follow-up until one year of age.

While the study analysis is primarily limited to prospective reports, retrospective reports will be carefully reviewed and used to assist with signal detection and summarized separately in the final reports.

9.10 OTHERS ASPECTS

None.

10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF THE INVESTIGATOR /HEALTH CARE PROVIDERS

The Investigator/Health Care Provider will perform the study in accordance with this protocol, applicable local regulations and international guidelines.

It is the Investigator /Health Care Provider's responsibility to obtain written informed consent from patients prior to inclusion in the study, to fill in the CRF and to record all data pertinent to the investigation. She/he will ensure that the information reported in the CRF is precise and accurate.

Investigator /Health Care Provider, and under the Health Care Provider's responsibility, should fully inform the Patient of all pertinent aspects of the study including the written information. All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the study, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or by the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form and the Information Sheet used by the Investigator/Health Care Provider for obtaining the Patient's Informed Consent must be reviewed and approved by the MAH/MAH representative prior to submission to the appropriate Independent Review Board/Ethics Committee (IRB/IEC) for approval/favorable opinion.

10.2 RESPONSIBILITIES OF MAH/MAH REPRESENTATIVE

The MAH/MAH representative is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

MAH/MAH representative is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

10.3 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.3.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

10.3.2 Laws and regulations

This study will be conducted in accordance with the guidelines for Good Epidemiology Practice (GEP) (13).

Each participating country should locally ensure all necessary regulatory submissions (e.g., IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

10.3.3 Data protection

The women's, infants', and their HCPs' personal data which may be included in the MAH/MAH representative study database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the women, infants, and HCPs, MAH/MAH representative shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.3.4 Insurance

Participating countries may contract insurance according to local specific requirements.

10.3.5 Secrecy agreement

All material, information (oral or written) and unpublished documentation provided to any third parties involved with the conduct of the study (or any action carried out by the MAH/MAH representative on their behalf), including the present protocol and the CRF, are exclusive property of the MAH/MAH representative.

These materials or information (both global and partial) cannot be given or disclosed by any third parties to unauthorized persons without the prior formal written consent of the MAH/MAH representative.

The National coordinator shall consider as confidential all the information received, acquired, or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

10.3.6 Record retention

The Study Coordinating Center shall arrange for the retention of study documentation until the end of the study. In addition the Study Coordinating Center will comply with specific local regulations/recommendations with regards to record retention for women and their infants.

The Study Coordinating Center shall arrange for retention of the study documents at least 5 years after the completion or discontinuation of the study, unless otherwise specified in the Study Coordinating Center Agreement in line with additional standards and/or local laws.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

10.3.7 Discontinuation of the study

The MAH/MAH representative can decide at any time and for any reason to discontinue the study; the decision will be communicated in writing to the participating Investigator.

Similarly, should the Investigator decide to withdraw from the study, she/he will have to inform the MAH/MAH representative in writing.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

10.3.8 MAH/MAH representative audits and inspections by competent authorities

The National coordinator involved with this study agree to allow the MAH/MAH representative auditors/Competent Authorities inspectors to have direct access to their study records for review, being understood that these personnel are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

The National coordinator will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be communicated by third parties to the MAH/MAH representative.

The national coordinator involved with this study shall take appropriate measures required by the MAH/MAH representative to take corrective actions for all problems found during the audit or inspections.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Spanning from the signature of the informed consent form until the end of the study as defined by the protocol, all serious adverse events (SAEs), including medically important events and pregnancy outcome related events (see Section 11.1.1), and non-serious AEs which potentially impact pregnancy outcome, will be collected by the HCP, submitted to the National Coordinator and reported to the MAH/MAH representative within expedited time frame (see Section 11.1.2.2).

Pregnancy related events, occurring BEFORE the signature of the informed consent for each patient are to be reported as part of the Pregnancy History.

11.1 SAFETY INSTRUCTIONS

11.1.1 Definitions of Adverse Event (AE) and Serious Adverse Event (SAE)

An **Adverse Event (AE**) is any untoward medical occurrence or clinical investigation in a patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

A **Serious Adverse Event** is an adverse event that at any dose:

- Results in death or;
- Is life-threatening or;
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;
- Is a congenital anomaly/birth defect;
- Is a medically important event;
- Suspected transmission of infectious agent; is any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination).

  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

For this study, SAEs also include specific pregnancy outcome related events: all spontaneous abortions, stillbirths, neonatal deaths, and foetal major malformations occurring in a LEMTRADA-exposed pregnancy.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events may include, but are not limited to malignancies, events requiring intensive treatment in an emergency room or at home, as allergic bronchospasm or convulsions, that do not result in inpatient hospitalization.

The following events should be reported in the same fashion as SAEs (within 24 hours within becoming aware of the event) if seriousness criteria, including "medically important" are met: autoimmune mediated conditions, including immune thrombocytopenia; thyroid disorders; other non-thyroid autoimmune diseases as nephropathies (including anti-glomerular basement membrane (anti-GBM) disease), cytopenias; serious infections (including serious opportunistic infections); pneumonitis, malignancy and symptomatic overdose (serious or non-serious) with LEMTRADA.

11.1.2 Obligations of the Investigator regarding safety reporting

11.1.2.1 Adverse Events collection

- All SAEs, including medically important events and pregnancy outcome related events.
- All non-serious AEs which to the opinion of HCP or National Coordinator may have an impact on the outcome of the pregnancy whether causally related to drug product or not.

11.1.2.2 Adverse event reporting to MAH/MAH REPRESENTATIVE

- **In case of Serious Adverse Events**

The National Coordinator will report to MAH/MAH representative Safety **within 24 hours of becoming aware** of an SAE, including medically important events and pregnancy outcome related events.

- **In case of Non Serious Adverse Events with potential impact on pregnancy outcome**

Adverse events should be reported by National Coordinator to MAH/MAH representative as soon as possible, not later than within **30 days of awareness**.

11.2 SAFETY OBSERVATIONS

- The Investigator should take all appropriate measures to ensure the safety of the patients as per normal practice.
- In case of any Serious Adverse Event (including medically important events and pregnancy outcome related events), the patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has finished regular study schedule.

11.3 OBLIGATIONS OF MAH/MAH REPRESENTATIVE

During the course of the study, the MAH/MAH representative will report safety data to health authorities according to Directive 2001/83/EC and in accordance with all applicable local and global regulations (e.g., All serious ADR within 15 days [calendar] from the date of receipt of the reports to the health Authorities; and if required for some European countries all non-serious ADR within 90 days [calendar] from the date of receipt of the reports to the health Authorities).

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the MAH/MAH representative conducting the study.

12.2 PUBLICATIONS

MAH is responsible for presentations and/or publications. The study results must be submitted to MAH for review before publication.

The final decision to publish any manuscript/abstract/presentation will be made by the Genzyme. All manuscript/abstract/presentation must be submitted to MAH at least 45 calendar days in advance of submission. MAH may request that the MAH's name and/or names of one or several of its employees appear or do not appear in such publication. In order to allow competent authorities to review in advance the results and interpretations to be published, the marketing authorisation holder initiating, managing or financing a non-interventional PASS should communicate to the Agency and the competent authorities of the Member States in which the product is authorised the final manuscript of the article within two weeks after first acceptance for publication.

MAH can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

13 REFERENCES

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14 APPENDICES

Appendix A Description of pregnancy outcomes

Each defect will be categorized using the CDC MACDP classification of birth defects (CDC MACDP, 1998). Major defects identified from the point of conception up to 1 year of age will be included in the analysis. Defects identified in any live birth will be considered in the primary analysis. Defects identified in any stillbirths or abortions (spontaneous or induced) will be considered in secondary analyses.

MACDP defines **major structural or genetic birth defects** as conditions that

1. result from a malformation, deformation, or disruption in one or more parts of the body, a chromosomal abnormality, or a known clinical syndrome;
2. are present at birth;
3. have a serious, adverse effect on health, development, or functional ability.

A **minor** structural defect is defined as a defect which occurs in less than 4 percent of the population but which has neither cosmetic nor functional significance to the child (e.g., complete 2,3 syndactyly of the toes).

Spontaneous abortion

Any loss of a fetus due to natural causes at ≤20 weeks gestation determined from the estimated date of conception or by ultrasound as spontaneous abortion. If available, information from gross or pathological examination of the abortus or fetus will be documented.

Induced abortion

Pregnancy termination is defined as any induced or voluntary fetal loss. If available, information from gross or pathological examinations will be documented.

Preterm birth

A live birth that occurs before 37 completed weeks of gestation determined from the estimated date of conception. Elective caesarian deliveries or inductions prior to 37 completed weeks will be analyzed separately.

Small for gestational age

Birth size (weight, length, or head circumference) ≤10th percentile for gender and gestational age using the NCHS pediatric growth curves for full term infants. Prenatal growth curves will be used for preterm infants.

Stillbirth

Any non-deliberate foetal death at >20 weeks gestation as estimated based on the estimated date of conception or by ultrasound.

Lost to follow-up

Enrolled women will be considered lost to follow-up if they are eligible, have provided informed consent, and have completed the initial intake interview but pregnancy outcome information is not available within 1 year of the estimated delivery date despite 4 attempts to obtain this information.

Appendix B List of stand-alone documents

None

OBS13436 Amended Protocol 02

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm)
[redacted]	GPE Approval	[redacted]
	Clinical Approval	
	Clinical Approval	
	Regulatory Approval	