A Multi-Country Cohort Database Study to Assess Pregnancy and Infant Outcomes in Women Exposed to Cladribine Tablets: CLEAR Study

K. Hellwig[1], M. Magyari[2], T. MacDonald[3], K. Gembert[4], S. Wergeland[5], M.K. Leinonen[6], A. Aydemir[7], M. Sabidó[8], A. Kawai[9], A. Arana[10]

[1]German MS and Pregnancy Register, Department of Neurology, St. Josef Hospital / Ruhr University, Germany; [2]Department of Neurology, Danish Multiple Sclerosis Center and The Danish Multiple Sclerosis Registry, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [3]MEMO Research, University of Dundee, Ninewells Hospital & Medical School, Dundee, Scotland; [4]Centre for Pharmacoepidemiology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [5]Norwegian MS Registry and Biobank, Department of Neurology, Haukeland University Hospital, Bergen, Norway; [6]Finnish Institute for Health and Welfare, Information Services Department, Helsinki, Finland; [7]EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA); [8]Merck Healthcare KGaA, Darmstadt, Germany; [9]RTI Health Solutions, Waltham, MA, USA; [10]RTI Health Solutions, Barcelona, Spain

CONCLUSIONS

The use of combined population-based data sources and registries will help to identify inadvertent exposure to cladribine tablets during pregnancy and assess pregnancy and infant outcomes with minimal loss to follow-up.

INTRODUCTION

- Cladribine tablets are contraindicated during pregnancy.
- CLEAR (EUPAS25027) is a cohort study that aims to assess the effect of cladribine tablets exposure on pregnancy and infant outcomes in pregnant women with multiple sclerosis (MS) and in pregnant women whose pregnancy is fathered by men with MS who received cladribine tablets.

CLEAR

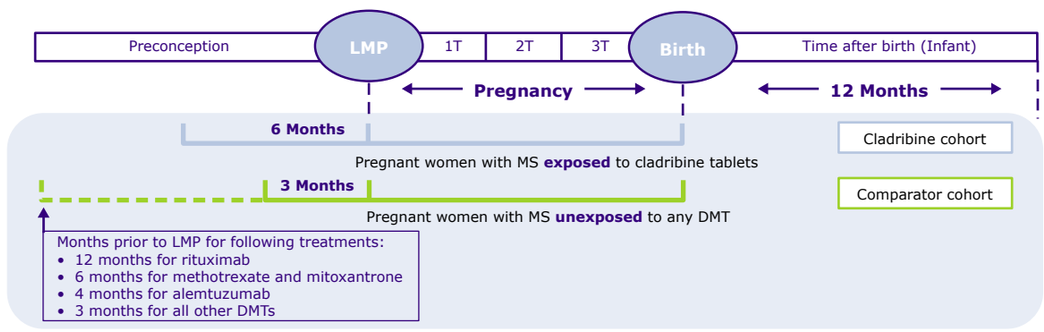
OBJECTIVES

To describe the study design of CLEAR and provide a study status update.

METHODS

Figure 1. Definition of Study Cohorts of Exposed and Unexposed Patients: Women with MS

- Pregnant women with MS are included in CLEAR if they have been:
  - Exposed to cladribine tablets during pregnancy, or within 6 months before last menstrual period (LMP)
  - Unexposed to any disease-modifying treatment (DMT) within the DMT-specific exposure windows



DMT, disease-modifying therapy, **LMP**, last menstrual period; **MS**, multiple sclerosis; **1T**, first trimester; **2T**, second trimester; **3T**, third trimester

Figure 2. Definition of Study Cohorts of Exposed and Unexposed Patients: Women Whose Pregnancy is Fathered by a Male Partner with MS

- Pregnancies exposed via a male partner with MS are included if the partner has been:
  - Exposed to cladribine tablets within 6 months before LMP
  - Unexposed to any DMT within the DMT-specific exposure windows

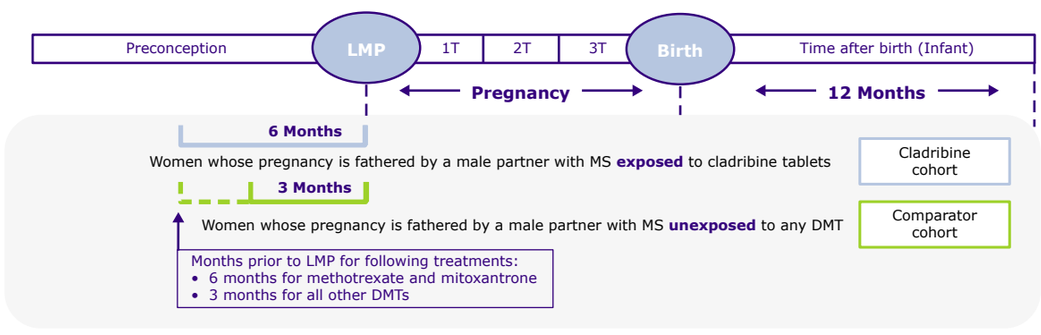


Figure 3. Study Outcomes

Primary Outcome

Occurrence of major congenital anomalies (assessed up age one year)
- Any
- By group, as defined by EUROCAT (e.g. organ system)

Secondary Outcomes

Pregnancy and maternal outcomes
- Spontaneous abortion
- Ectopic pregnancy
- TOPFA
- TOPMR*
- Stillbirth
- Maternal death*

Outcomes at birth
- Low birth weight
- Small for gestational age
- Large for gestational age
- Birth length (low)
- Birth weight (very low vs not very low; low vs not low; high vs not high)

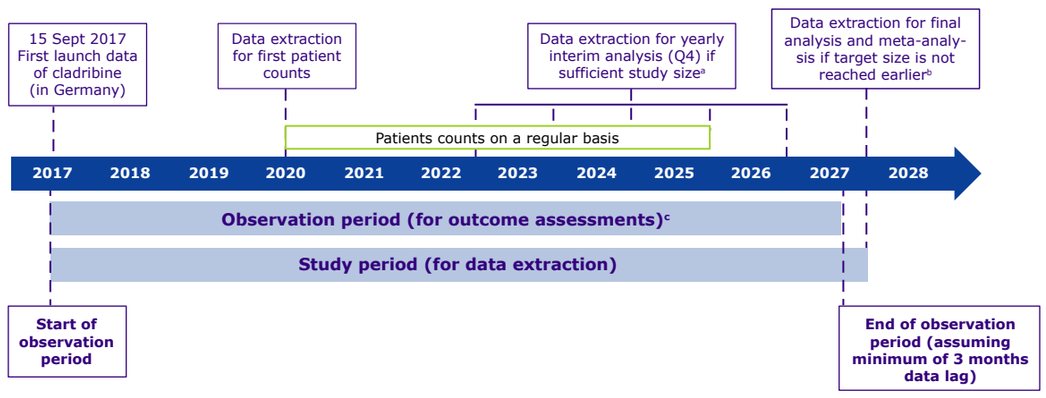
Neonatal and infant outcomes
- Neonatal death
- Post neonatal death
- Infant death

Exploratory Outcomes

- Growth measurements at 3 months and at 12 months:
  - Length
  - Weight
  - Head circumference
- Hearing loss (assessed up to age one year)

*Only for pregnancies in female patients with MS. †Not all exploratory outcomes will be available in all data sources.
MS, multiple sclerosis; **TOPFA**, termination of pregnancy due to fetal anomaly; **TOPMR**, termination of pregnancy due to maternal risk

Figure 4. Study Time Frame



[a]The first interim analysis will be conducted when at least 75 pregnant women (25 pregnant women with MS exposed to cladribine tablets and 50 women with MS unexposed to any DMT) have been included in a specific country. Additional interim analyses will be conducted each time 25 additional pregnant women with MS exposed to cladribine tablets and 50 pregnant women with MS unexposed to any DMT have been included in a specific country. [b]The target study size is 134 live births from 149 pregnant women with MS exposed to cladribine tablets and 268 live births from 298 pregnant women with MS unexposed to any DMT in all countries combined. [c]Start and end of the observation period will vary by country, depending on the launch date of cladribine tablets and the data source–specific data lags.

DMT, disease-modifying therapy; **LMP**, last menstrual period; **MS**, multiple sclerosis

METHODS (continued)

- Pregnancies will be followed until the outcome of the pregnancy is known, and live births will be followed for up to one year of age.
  - For major congenital anomalies analyses, only pregnancies that have one year of observation available following birth will be included.
- The study aims to include 447 pregnant women with MS (149 exposed; 298 unexposed) from the participating registries/data sources by the end of expected data collection period (December 2027).
- Separately in pregnant women with MS and in pregnancies fathered by men with MS, adjusted (if outcome numbers permit) and unadjusted odds ratio of outcomes will be estimated within each data source, comparing participants exposed to cladribine tablets versus unexposed.
- A meta-analysis pooling aggregated results from each data source will be performed.

RESULTS

- By March 2021, 307 pregnancies (9 exposed, 298 unexposed) had been identified from the following sources:
  - German MS Pregnancy Registry
  - MEMO Research MS data and Public Health data in Scotland
  - Nordic national health registers linked or not with MS registries
    - Denmark
    - Finland
    - Norway
    - Sweden
- The first interim report from the CLEAR study is planned for Q4 2023.

Disclosures: KH has received honoraria and research support from Bayer, Biogen, Merck, Novartis, Sanofi-Genzyme, and Teva. **MM** has served on scientific advisory board for AbbVie, Alexion (Janssen/J&J), Biogen, Merck, Novartis, Roche, and Sanofi, and has received honoraria for lecturing from Biogen, Merck, Novartis, and Sanofi, and has received support for congress participation from Biogen, Genzyme, Merck, and Roche. **TMacD** MEMO Research has done funded research with Menarini and is assisting AstraZeneca with the design and public engagement of trial software. **TMacD** currently advises Novartis. **KG** has no conflicts of interest. **SW** has served on scientific advisory boards for Biogen, Novartis, and Sanofi, and has received honoraria for lecturing from Biogen and Novartis, and are currently engaged in sponsor-initiated research by Biogen, EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA), and Merck. **MKL** has no conflicts of interest. **AAy** is an employee of EMD Serono Research & Development Institute, Inc., Billerica, MA, USA (an affiliate of Merck KGaA). **MS** is an employee of Merck Healthcare KGaA, Darmstadt, Germany. **AK** and **AAr** are employees of RTI Health Solutions. The RTI authors participated in this work in the course of employment as work for hire, pursuant to a contract to conduct an independent research study for Merck. The authors received no compensation other than their annual salary from their employer.

Medical writing assistance was provided by Joseph Ward of inScience Communications, Springer Healthcare Ltd, UK, and was funded by Merck Healthcare KGaA, Darmstadt, Germany.

CLEAR study: EU PAS Register No. EUPAS25027.

Presented at ECTRIMS 2021 Virtual Congress | 13–15 October

Data collection and analysis was sponsored by Merck (CrossRef Funder ID: 10.13039/100009945)