Pregnancy outcomes in women exposed to oral cladribine: a multi-country cohort database study (CLEAR)

First published: 24/08/2018

Last updated: 28/04/2025

Study Ongoing

Administrative details

EU PAS number

EUPAS25027

Study ID

49924

DARWIN EU® study

No

Study countries

- ☐ Denmark
- ☐ Finland
- ☐ France
- ☐ Germany

- [ ] Norway
- [ ] Sweden
- [ ] United Kingdom

Study description

The design of this pregnancy PASS is a cohort study based on secondary use of data from various automated healthcare databases (AHDB) and registers in 6 European countries: Denmark, Finland, France, Germany, Norway, Sweden, and Scotland (United Kingdom).

Women with Multiple Sclerosis (MS) who were exposed to oral cladribine during pregnancy and/or within 6 months before their last menstrual period (LMP) (i.e. exposure period, which correspond to the at-risk period for pregnancy outcomes, major congenital anomalies (MCA) in infants), or pregnancies fathered by men with MS treated with oral cladribine within 6 months before the LMP, will be identified in the selected databases/registers. Data will be retrieved on pregnancies and their outcomes, and infants for MCA, and hearing loss.

Comparison of pregnancy outcomes will be conducted in pregnant women with MS between the exposed cohort (exposure to oral cladribine within the at-risk period) and the unexposed cohort (unexposed to any Disease-modifying drug [DMD] during the at-risk period, which can vary from 3 to 24 months according to the DMD) and in pregnant women whose pregnancy is fathered by men with MS between the exposed cohort (pregnancy fathered by men with MS exposed to oral cladribine within the at-risk period) and the unexposed cohort (pregnancy fathered by men with MS unexposed to any DMD during the at-risk period, which can vary from 3 to 6 months before the LMP according to the DMD .

In the selected data sources, pregnancies will be followed until the outcome of the pregnancy is known, and live births resulting from an identified pregnancy will be followed for up to one year of age.

Study status

Ongoing

Research institutions and networks

Institutions

RTI Health Solutions (RTI-HS)

- [ ] France
- [ ] Spain
- [ ] Sweden
- [ ] United Kingdom
- [ ] United Kingdom (Northern Ireland)
- [ ] United States

First published: 21/04/2010

Last updated: 13/03/2025

Institution **Not-for-profit** **ENCePP partner**

Centre for Pharmacoepidemiology, Karolinska Institutet (CPE-KI)

- [ ] Sweden

First published: 24/03/2010

Last updated: 23/04/2024

Institution **Educational Institution** **Laboratory/Research/Testing facility** **Not-for-profit** **ENCePP partner**

MEMO Research, University of Dundee

United Kingdom (Northern Ireland)

First published: 12/05/2010

Last updated: 17/05/2024

Institution | Educational Institution | Not-for-profit | ENCePP partner

Drugs and Pregnancy, Finnish Institute for Health and Welfare (THL)

Finland

First published: 17/03/2010

Last updated: 20/03/2024

Institution | Educational Institution | Laboratory/Research/Testing facility | ENCePP partner

Department of Neurology, Haukeland University Hospital, Bergen, Norway; Department of Clinical Medicine, University of Bergen, Bergen, Norway; Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; Hospices Civils de Lyon, Service de Neurologie,

Sclérose en Plaques, Pathologies de la Myéline et Neuro-Inflammation—Hôpital Neurologique Pierre Wertheimer, Bron Cedex, France;
Department of Neurology, St. Joseph and St. Elisabeth Hospital, Ruhr University, Bochum, Germany

Contact details

Study institution contact

Communication Center Merck Healthcare KGaA

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Study contact

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Primary lead investigator

Alejandro Arana

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 20/12/2018

Actual: 09/09/2019

Study start date
Planned: 31/12/2020

Actual: 14/12/2020

Data analysis start date
Planned: 31/12/2027

Date of interim report, if expected
Planned: 31/12/2024

Actual: 12/11/2024

Date of final study report
Planned: 31/12/2028

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Merck Healthcare KGaA

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

EU RMP category 3 (required)

Methodological aspects

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Main study objective:

To estimate prevalence of major congenital anomalies among infants of women with MS exposed to oral cladribine during and/or 6 months prior to pregnancy, and compare with prevalence in infants of pregnant women with MS unexposed to any disease modifying drug during or 3 months prior to pregnancy.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Medicinal product name

MAVENCLAD

Study drug International non-proprietary name (INN) or common name

CLADRIBINE

Anatomical Therapeutic Chemical (ATC) code

(L04AA40) cladribine

cladribine

Medical condition to be studied

Multiple sclerosis

Population studied

Short description of the study population

This study will enroll participants in a ratio of 1:2 between the cohort of pregnant women with Multiple Sclerosis (MS) exposed to oral cladribine to the cohort of pregnant women with MS unexposed to any DMD.
Thus, aim is to enroll a total of 447 pregnant woman with 149 pregnant women with MS exposed to oral cladribine and 298 pregnant women with MS unexposed to any DMD.
If the targeted sample size is not reached 5 years after the first feasibility check (pregnancy counts in the maternal cohort) in the study, recruitment will be stopped.

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)

Special population of interest

Pregnant women

Estimated number of subjects

447

Study design details

Outcomes

Primary: Ocurrence of MCA (any and by type)

Secondary: Occurrence of pregnancy outcomes(any)including spontaneous abortions; ectopic pregnancies; terminations of pregnancy due to foetal anomaly (TOPFA); terminations of pregnancy due to maternal risk (TOPMR)*; stillbirths: neonatal death; post-neonatal infant death, infant death and maternal death*

Occurrence of alterations in growth evident in foetuses at birth (eg,low birth weight [LBW], small for gestational age [SGA])

*only for pregnancies in female MS patients

Data analysis plan

For each country, study variables will be described by study cohort.

These variables will be used as potential confounders (if relevant) when comparing pregnancy outcomes between study cohorts.

Descriptive statistics including number of outcomes (n) and prevalence (%, with corresponding 95% confidence interval [CI]) will be presented for each pregnancy outcome in each study cohort separately.

The prevalence rate and prevalence difference between exposed and unexposed cohorts will be reported with corresponding 95%CI.

In each country, prevalence of pregnancy outcomes will be further compared between study cohorts using logistic regression with adjustments for potential confounders.

The odds ratio (OR) estimates with 95% CI will be reported for these comparisons.

Impact of exposure on each outcome will be assessed by stratification on timing of exposure (exposure will be categorized into trimesters based on cladribine start and stop dates) and on maternal age at LMP: Meta-analysis using aggregated results from each country database analysis will be performed.

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data source(s), other

Nordic health registers from Denmark, Finland, Norway, and Sweden;
Danish Multiple Sclerosis Registry, Denmark;
Norwegian MS-registry and Biobank, Norway;
German Multiple Sclerosis and Pregnancy Registry, Germany;
French Registry for Monitoring Pregnancies for MS (RESPONSE), France;
The Public Health Scotland Datasets, Scotland

Data sources (types), other

Prospective study based on secondary use of data from various automated healthcare databases (AHDB) and registers

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No