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A multi-country cohort database study to assess pregnancy and infant outcomes after potential maternal or paternal exposure to cladribine tablets in the treatment of multiple sclerosis: the CLEAR study methods and status update

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Kerstin Hellwig, Melinda Magyari, Thomas M. MacDonald, Carolyn E. Cesta, Stig Wergeland, Maarit K. Leinonen, Asher Ornoy, Sandra Vukusic, Alexandra Lauer, Xiaolei Zhou, Alison Kawai, Rachel Weinrib, Alejandro Arana and Tahani Boumenna

Abstract

Background: Cladribine tablets are contraindicated during pregnancy; therefore, safety data on pregnancies exposed to this treatment are limited. CLEAR collects and describes pregnancy outcomes in this understudied population.

Objectives: To describe the main features of the CLEAR study design, including the data sources and the methodological approach, and provide a status update.

Design: CLEAR is a non-interventional, multi-database, comparative cohort study. Four cohorts are included: pregnancies of women with multiple sclerosis (MS) exposed to cladribine tablets (maternal cohort exposed); pregnancies of women with MS unexposed to any disease-modifying therapy (DMT; maternal cohort unexposed); pregnancies fathered by men with MS exposed to cladribine tablets; and pregnancies fathered by men with MS unexposed to any DMT.

Methods: A staggered methodological approach, using data from Denmark, Finland, France, Germany, Norway, Scotland, and Sweden, will be applied to analyze the occurrence of major congenital anomalies (primary outcome) and selected pregnancy outcomes. The first interim analysis (performed using German pregnancy cohorts) was conducted when ⩾75 pregnant women (including 25 women from the maternal cohort exposed) were cumulatively reached across all participating countries. The end of the study period will be established once pregnancy counts reach 149 in the maternal cohort exposed and 298 in the maternal cohort unexposed in all countries combined, or 5 years after pregnancy counts are first assessed (whichever occurs first).

Results: As of January 2024, data on pregnancies of women exposed to cladribine tablets ($n = 28$–36 (numbers are approximate due to masking of some counts)), and pregnancies of women unexposed to cladribine tablets ($n = 2834$) were available from Denmark, Finland, Germany, Scotland, and Sweden.

Conclusion: The CLEAR study, using a staggered methodological approach, aims to provide further insight into the safety outcome data for cladribine tablets in pregnant women, as a regulatory commitment with the European Medicines Agency.

Trial registration: EU PAS Register number, EUPAS25027.

Correspondence to:
Kerstin Hellwig
German MS and Pregnancy Register, Department of Neurology, St. Josef Hospital/Ruhr University, Bochum, Gudrunstrasse 56, Bochum 44791, Germany
kerstin.hellwig@rub.de

Melinda Magyari
The Danish Multiple Sclerosis Registry, Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Glostrup, Denmark

Danish Multiple Sclerosis Center, Department of Neurology, Copenhagen University Hospital, Rigshospitalet, Glostrup, Denmark

Institute for Clinical Medicine, University of Copenhagen, Copenhagen, Denmark

Thomas M. MacDonald
MEMO Research, Dundee University, Ninewells Hospital, Dundee, Scotland

Carolyn E. Cesta
Centre for Pharmacoepidemiology, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden

Stig Wergeland
Norwegian MS Registry and Biobank, Department of Neurology, Haukeland University Hospital, Bergen, Norway

Department of Clinical Medicine, University of Bergen, Bergen, Norway

Maarit K. Leinonen
Knowledge Brokers, Finnish Institute for Health and Welfare, Helsinki, Finland

Teratology Information Service, Emergency Medicine and Services, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Asher Ornoy
Department of Medical Neurobiology, Hebrew University Hadassah Medical School, Jerusalem, Israel

Adelson School of Medicine, Ariel University, Ariel, Israel

Sandra Vukusic
Department of Neurology, Multiple Sclerosis, Myelin Pathologies and Neuro-Inflammation, Pierre Wertheimer Hospital, Bron, France

Center for Research in Neuroscience in Lyon, INSERM 1028 and CNRS UMR 5292, Observatoire Français de la Sclérose en Plaques (OFSEP), Lyon, France

Claude Bernard University Lyon 1, Villeurbanne, Lyon, France

Alexandra Lauer
Biostatistics, Merck Healthcare KGaA, Darmstadt, Germany

Xiaolei Zhou
Alison Kawai
RTI Health Solutions, Research Triangle Park, NC, USA

Rachel Weinrib
Alejandro Arana
RTI Health Solutions, Barcelona, Spain

Tahani Boumenna
EMD Serono Research & Development Institute, Inc., Billerica, MA, USA, an affiliate of Merck KGaA

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Background

Multiple sclerosis (MS) is usually diagnosed in individuals aged 20–40 years and is the most common neuroimmunological disease in females of childbearing age.[1,2] The effective management of MS before or during pregnancy is challenging, because certain disease-modifying therapies (DMTs) are contraindicated, or not recommended, during this period due to possible risks associated with fetal toxicity, discontinuation rebound,[3] and the paucity of safety data in this population.[4] Reproductive considerations are therefore important for both women and men with MS who are planning to conceive and are receiving DMTs with pregnancy-related warnings.[5] The use of reliable contraception is required during treatment with cladribine tablets and for at least 6 months after the last dose, with a negative pregnancy test required before the start of the first and second yearly treatment course of cladribine tablets, although several pregnancies have been reported within this time period.[6–9] Of note, data are limited on pregnancies where the mother and/or father were treated with cladribine tablets. Through the use of a cohort design (comparing exposed and unexposed pregnancies) in both pregnant women with MS and in pregnancies fathered by men with MS (where these data are available), the CLEAR study aims to provide insight into the safety of cladribine tablet use in these relatively unstudied populations.

A published analysis of pregnancy outcomes in the cladribine clinical development program reported no congenital anomalies in 16 pregnancies that occurred during cladribine treatment or within 6 months after the last dose, and there was no imbalance in adverse pregnancy outcomes between patients receiving cladribine and placebo.[6] However, data were only available for a limited number of pregnancies (3 live births; 10 elective terminations; 2 spontaneous abortions (SAs); and 1 therapeutic termination)[6]; therefore, a larger sample size is needed to assess the possible effects of cladribine on pregnancy outcomes.

In the data from the German MS and Pregnancy Registry (reporting pregnancies with women exposed and unexposed to cladribine tablets between November 2018 and April 2022), one major congenital anomaly (MCA; an atrial septum defect) was reported out of 27 live births, following maternal exposure to cladribine tablets within 6 months prior to pregnancy; no SAs or stillbirths (SBs) were reported.[7] Recent data from the worldwide pregnancy surveillance program of oral cladribine (MAPLE-MS) (cut-off 01 April 2023; $n = 59$) reported one incident of MCA (both the incident and case were identical to that reported in the German MS and Pregnancy Registry above[7]) in pregnancies with known outcomes after maternal exposure to cladribine tablets (from the live birth cohort excluding genetic anomalies). No cases of MCA were reported in the paternally exposed cohort ($n = 13$). SAs were reported in pregnancies, where the woman was exposed (20.0%) and where the father was exposed (15.4%). Ectopic pregnancy occurred in 1.8% of pregnancies, where only the woman was exposed.[10] The prevalence of MCAs is consistent with those seen in the overall general population unexposed to cladribine, where SAs are reported in around 10%–20% of pregnancies, and may be up to 31% when including early miscarriages occurring before a woman realizes she is pregnant.[11,12] Additionally, ectopic pregnancy occurs in around 1%–2% of the overall population.[13]

Due to the limited availability of data for pregnancies where either the woman with MS or father with MS was exposed to cladribine tablets, the CLEAR study (EUPAS25027; EMA Study ID: 49924)—a noninterventional postauthorization safety study based on secondary use of data from various automated healthcare databases and registries—has been initiated, as a regulatory commitment with the European Medicines Agency (EMA). The objectives of this manuscript are to describe the CLEAR study design, including the data sources and the specific staggered methodological approach implemented in the

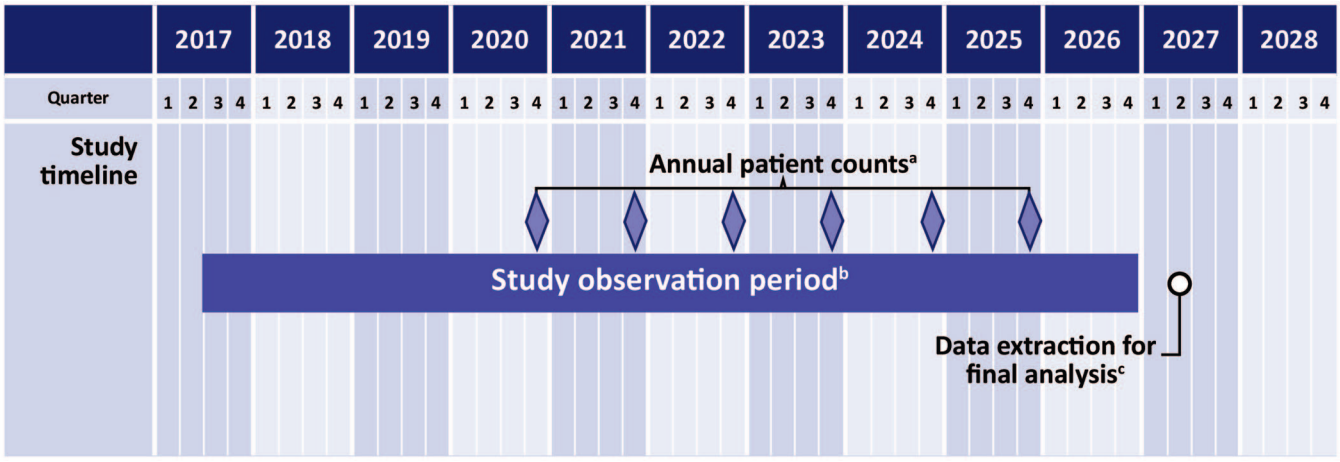

Figure 1. Illustration of the timeframe for the CLEAR study.
[a]The first interim analysis (performed using the German data) was conducted when at least 75 pregnant women (25 pregnant women with MS exposed to cladribine tablets and 50 women with MS unexposed to any DMT) were cumulatively reached across all participating countries. 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 cumulatively reached across all participating countries.
[b]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.
[c]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. If target study size is not met, the end of the study period will be 5 years after pregnancy counts are first assessed.
DMT, disease-modifying therapy; MS, multiple sclerosis.

CLEAR study, as well as to provide a status update.

Methods

Study design

CLEAR is a noninterventional comparative cohort study that aims to assess the effect of cladribine tablets exposure (6 months before the start of pregnancy—defined by the last menstrual period (LMP)—and/or during pregnancy) on pregnancy and infant outcomes in pregnant women with MS, and (where data are available) in pregnant women whose pregnancy is fathered by men with MS who received cladribine tablets within the 6 months prior to conception. The study is based on the secondary use of data from healthcare databases, registers, and registries from seven European countries: Denmark, Finland, France, Germany, Norway, Scotland (United Kingdom), and Sweden. Figure 1 presents the study timeframe and design. The proposed 6-month exposure period corresponds to the susceptible prepregnancy window for pregnancy outcomes or MCAs in infants, according to the cladribine tablets label. This window allows 3 months for the completion of a follicular or spermatogenic cycle, with an additional precautionary 3 months added during the development of the prescribing information for cladribine tablets.[6]

Data will be retrieved on pregnancies from a cohort of women or fathers with MS, including maternal, at birth, and infant/neonatal outcomes. Each exposed cohort will be compared to cohorts of pregnancies where neither the woman nor the father was exposed to any DMT. Pregnancies will be assessed from the date of the LMP (index date) until the outcome of the pregnancy is known, and live births resulting from identified pregnancies will be followed for up to 1 year of age. A follow-up of 1 year was chosen to assess the occurrence of hearing loss in infants (an exploratory outcome) and to capture MCAs recorded up to 1 year of age in Denmark, Finland, France, Germany, Scotland, and Sweden.[14] In certain Nordic countries, data have indicated that 1 year of follow-up is sufficient to capture most MCAs.[14]

Study outcomes

A list of the relevant data sources in different countries by study outcome, exposure, and MS population is shown in Table S1. In Germany, all

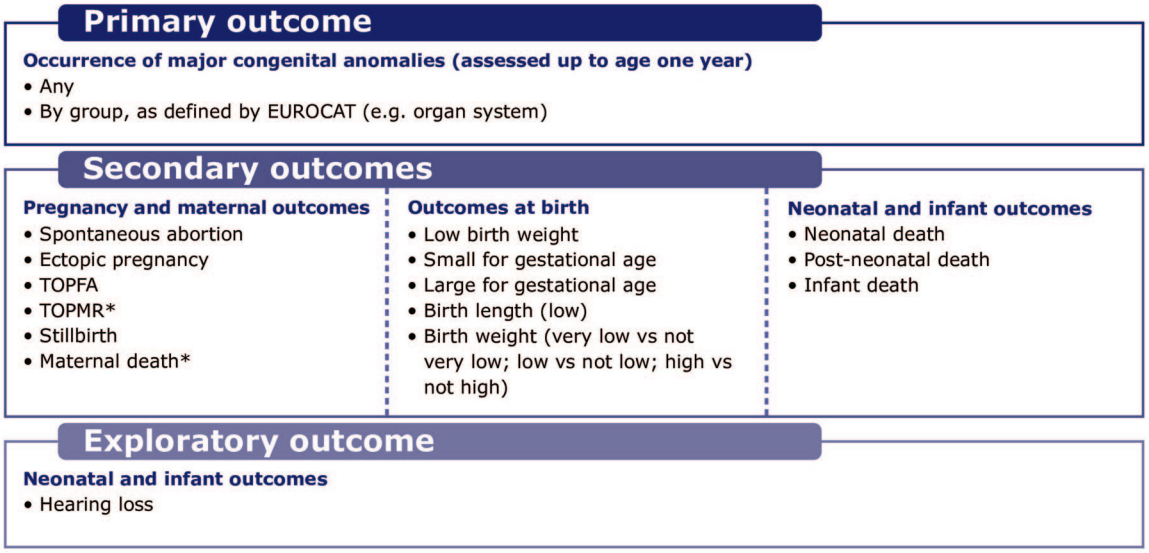

Figure 2. Summary of the primary, secondary, and exploratory outcomes of the CLEAR study.
*Only for pregnancies in female patients with MS.
EUROCAT, European Surveillance of Congenital Anomalies; MS, multiple sclerosis; TOPFA, termination of pregnancy due to fetal anomaly; TOPMR, termination of pregnancy due to maternal risk.

data are obtained from the MS pregnancy registry.

The primary outcome is the occurrence of any MCA identified in liveborn and stillborn infants either during pregnancy, or within the first year after birth; EUROCAT MCA subgroup and group will also be described, and all are defined as per the EUROCAT Guide (Version 1.5; updated June 2022). MCA refers to a major congenital/fetal structural anomaly, teratoma, and congenital hypothyroidism involved in a birth. MCAs do not include hereditary diseases and other diseases not associated with congenital anomalies, dysfunction of organs or tissues, developmental disabilities, congenital infections, isolated minor dysmorphic features, normal variations, common less significant congenital anomalies, transient abnormalities, positional defects, or prematurity-related anomalies. Minor anomalies will be excluded according to the EUROCAT Guide (Version 1.5; updated June 2022). Genetic anomalies/disorders (e.g., skeletal dysplasia and chromosomal anomalies) will not be included in the definition of MCA for this study. MCA outcome data provided by the Register of Congenital Malformations in Finland are currently only available for analysis 2 years after the birth year, as birth data are released for the whole cohort at the same time. All study outcomes are presented in Figure 2.

The secondary outcomes are the prevalence of: SAs; ectopic pregnancies; termination of pregnancy due to fetal anomaly; SBs; neonatal death; postneonatal death; infant death; growth restriction evident at birth (live births only (low birth length; very low birth weight; low birth weight; high birth weight; low birth head circumference; small size for gestational age; large size for gestational age)). The single exploratory outcome is hearing loss.

Staggered methodological approach

Due to an anticipated low number of pregnancies with a woman or father exposed to cladribine tablets (in view of label recommendations), the CLEAR study utilizes a staggered methodological approach to monitor pregnancy counts to inform if there are a sufficient number of pregnancies to proceed with the analysis of pregnancy and infant safety outcomes (Figure 3). The study monitors patient counts accrued each year in each data source for the number of pregnancies of women with MS exposed to cladribine tablets (maternal cohort exposed) and the pregnancies of women with MS unexposed to any DMT (maternal

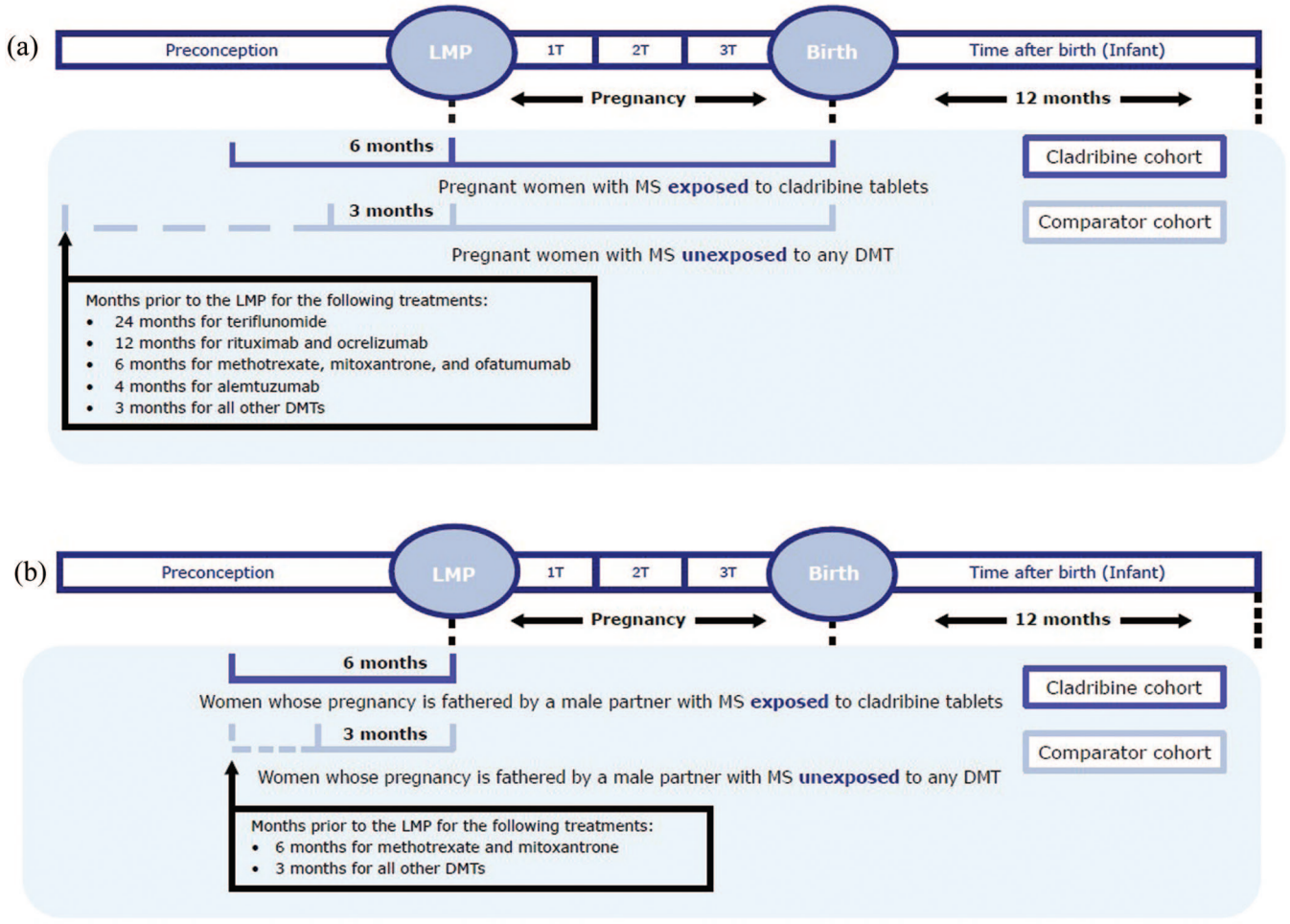

Figure 3. Study design and definition of exposed and unexposed study cohorts. (a) Pregnant women with MS are included in CLEAR if they have been: (i) Exposed to cladribine tablets during pregnancy, or within 6 months before the LMP. (ii) Unexposed to any DMT within the DMT-specific exposure windows. (b) Pregnancies with an exposed father with MS are included in CLEAR if the father has been: (i) Exposed to cladribine tablets within 6 months before the LMP. (ii) Unexposed to any 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.

cohort unexposed (list of DMTs in Table S2)). Additionally, the number of pregnancies ending in live births for the exposed and unexposed cohorts are accrued each year by country.

The first interim analysis (performed using German pregnancy counts) was 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) were cumulatively reached across all participating countries. Further analyses will only be performed in a particular country if it has reached at least 10 pregnancies with a woman exposed (countries with less than 10 exposed pregnancies at the time of the interim analysis will report only monitoring counts and no outcome numbers). The analysis for the interim report is mostly descriptive, reporting pregnancy outcome counts in the exposed/unexposed cohorts without any comparative measures.

The end of the study will be established once pregnancy counts reach 149 in the maternal cohort exposed and 298 in the maternal cohort unexposed in all countries combined, or 5 years after pregnancy counts are first assessed (whichever occurs first). The end of observation of outcomes that do not require follow-up after birth is expected in December 2025, with data extraction

for the final analysis expected in Q1 2027 (March 31, 2027). The target study sizes were calculated to obtain data on 134 live births exposed to cladribine tablets and 268 live births unexposed to cladribine tablets, to ensure the analyses were adequately powered to detect the effect size of exposure to cladribine tablets for the primary outcome, MCA. These target sizes were based on the assumption that 90% of all enrolled pregnancies will result in the birth of a live infant.[15,16] This 1:2 ratio was selected due to the expectation of more recordings of pregnant women unexposed than exposed, as pregnancy during treatment with cladribine tablets is contraindicated. These numbers will provide a 95% (two-sided) confidence interval in the range of 1.002–3.994, assuming a proportion of 5.5% MCAs in the unexposed group and an observed relative risk of 2. Comparative analyses will be conducted at the time of the final analysis.

No target pregnancy count has been determined for pregnancies where the father was exposed, as counts are expected to be low. Analyses of pregnancies fathered by men with MS exposed to cladribine tablets (paternal cohort exposed), will be performed at the final analysis and will be descriptive only. Data for the paternal cohort exposed are not available for Germany, France, and Scotland.

Data sources

For inclusion in the study, participating data sources were required to: capture the study population (pregnant women with MS); capture the exposure to DMTs (during/prior to pregnancy start); capture the relevant study outcomes and the main covariates, directly or through linkage; capture follow-up data on the infant through the first year after birth; be population-based or a disease-pregnancy registry, and currently active. Data on paternal exposure to cladribine tablets in the pre-conception period were available from some of the participating countries; however, this was not a prerequisite for inclusion in this study. Further information on outcome sources for all participating countries can be found in Table S1.

MS registry data linked with national health registers in Nordic countries (Denmark, Finland, Norway, and Sweden). The Danish, Finnish, Norwegian, and Swedish national health registers are extensive nationwide population-based databases that can be linked through a patient's unique personal identification number (PIN) and cover healthcare settings, hospital outpatient prescription databases, and death registers. The national patient registries for Denmark, Norway, and Sweden have undergone extensive validation; however, diagnostic completeness (relative to the general population) is low for conditions treated by a general practitioner (i.e., conditions not requiring hospitalization) and the use of prescription data, and other databases is recommended to improve completeness.[17] For MS diagnosis, the MS registers in Denmark, Norway, and Sweden will be used. In Finland, information on maternal and paternal MS diagnoses will be obtained from the Register on Medical Special Reimbursements. All Nordic Medical Birth Registers (MBRs) provide information on mothers and infants using patient PINs. All of the Nordic MBRs include data on live versus SB; abortions are not registered (except elective abortions in Denmark). Certain MBRs also collect information on fertility treatments (all Nordic MBRs), indications (the Norwegian MBR), and procedures (the Norwegian and Swedish MBRs).[17]

From the Nordic countries, both the father and their exposure to cladribine tablets can be identified, making it possible to assess exposure preconception by men with MS and link it to pregnancy outcomes. In Denmark and Norway, the MBR includes the fathers' PIN, allowing individual-level linkage with both liveborn and stillborn infants. However, paternity is not biologically confirmed (it is either assumed or confirmed by signature), and identifying all fathers is not possible; paternity is not recorded for pregnancies terminated due to birth defect or health problems for the child.

RESPONSE Registry (France). In France, a national prospective multicenter pregnancy registry for women with MS (RESPONSE), nested within the Observatoire Français de la Sclérose en Plaques (OFSEP), was established in August 2019 and holds information on pregnant women with MS and their children. Data recorded by OFSEP contain information such as the clinical evaluation of the patients, the DMTs used to treat MS, and results of magnetic resonance imaging. Pregnancy data recorded include pregnancy outcomes and infant health data, such as birth weight,

congenital abnormalities, developmental, and/or functional disabilities, and alterations in growth, until 6 years of age.

German MS pregnancy registry (Deutsches Multiple Sklerose und Kinderwunsch Register). This registry provides comprehensive data of pregnancies in women with MS that is collected via standard questionnaires. Less than 5% of the patients are lost to follow-up at the end of the pregnancy, and less than 10% of the infants are lost to follow-up at 12 months of age. Unlike the other data sources, which are population-based, enrolment of pregnant women into this registry is voluntary, with women providing signed informed consent to enroll.

Public Health Scotland datasets. Public Health Scotland (PHS) datasets comprise generalized healthcare data for the whole of Scotland and are linked with the Scottish Birth Record, National Record of Scotland (NRS) deaths data, NRS Infant Deaths, NRS Stillbirths, Prescribing Information System for Scotland, hospital inpatient and day case admissions data, maternity data (covering inpatient and day cases), and national cancer registry. Linkage of data and analysis are performed by an academic group (MEMO Research) operating within the University of Dundee.

In Scotland, DMTs are dispensed in hospital pharmacies only. Currently, the development of a nationwide hospital prescription database is planned. This database will be used if available before the time of the final data report for CLEAR. Otherwise, MS prescribing data will be extracted from local centers using the medical records of neurologists and transmitted to PHS for linkage with other datasets.

Study population

Inclusion criteria. Women will be included in the study if they fulfill one of the following criteria (Figure 3):

Maternal cohort exposed: pregnancies of women with MS who have been dispensed or used at least one dose of cladribine tablets during pregnancy and/or became pregnant (counted from the first day of the LMP) within 6 months after the last date of cladribine tablets being dispensed or used.

Paternal cohort exposed: pregnancies fathered by men with MS who have been dispensed or used at least one dose of cladribine tablets within the 6 months before conception.

Maternal cohort unexposed: pregnancies of women with MS who have not been dispensed or used any DMT during pregnancy or at least 3 months before the conception.

Paternal cohort unexposed: pregnancies fathered by men with MS who have not been dispensed or used any DMT within 3 months before the woman's LMP.

The following exceptions were also included within the maternal cohort unexposed: 24 months before the LMP for teriflunomide; 12 months for rituximab and ocrelizumab; 6 months for methotrexate, mitoxantrone, and ofatumumab; and 4 months for alemtuzumab. For the paternal cohort unexposed, exceptions were 6 months before the LMP for methotrexate and mitoxantrone. Table S2 presents the list of DMTs included in the study, corresponding brand names, and whether they are administered in hospital only or not.

Exclusion criteria. Women who were not continuously enrolled in the database for at least 12 months before the date of the LMP are not eligible for inclusion in the study (applicable to the PHS datasets only).

Statistical analysis

In the interim analysis, descriptive measures (counts and percentages) of outcomes by cohort will be summarized within each country. The number of events (n) and the prevalence (%, 95% confidence intervals) will be presented for each study outcome in each cohort separately. No comparative analyses will be conducted. Crude and adjusted analyses will be conducted only in the final analysis.

For the final analysis, the adjusted odds ratio (OR) of outcomes will be estimated (separately in pregnant women with MS and in pregnancies fathered by men with MS) using logistic regression with overlap weighting. Covariates will be included for adjustment in the multivariable logistic regression, or propensity score model,

based on the magnitude of their OR in the outcome model (e.g., the crude OR is greater than 1.25 or less than 0.80) using infants born from women with MS (for MCA and other infant outcomes) or pregnancies of women with MS (for pregnancy outcomes). Selected covariates may be different across countries and may be adjusted based on clinical relevance. The selected covariates will be adjusted for in the model (if outcome numbers permit) within each data source; the multivariable logistic regression model will be used to compare participants exposed to cladribine tablets versus those unexposed. A full list of possible covariates is available in Table S3. The main analysis for MCA does not require 1 year of follow-up (a separate sensitivity analysis will require 1 year of follow-up in liveborn infants). Pregnancy exposure will be described by trimester of pregnancy as follows: pre-LMP; first trimester (1T); second trimester (2T); third trimester (3T); or unknown. The pre-LMP period was defined as the time window for which the exposure to oral cladribine or another DMT might be considered at risk of adverse pregnancy or infant outcomes and ends at the date of the LMP. Notably, the duration of the pre-LMP period varies according to the type of DMT. The pregnancy trimesters are defined as follows: 1T = From date of LMP to date of LMP + 90 days, 2T = from date of LMP + 91 days to date of LMP + 188 days, 3T = from date of LMP + 189 days onwards.[18] Timing of exposure to cladribine tablets will be further categorized as follows: pre-LMP; 1T; only after 1T; and unknown.

The final analysis will include descriptive and comparative analyses performed at each research center and a fixed-effects meta-analysis to provide an adjusted estimate of the OR of MCA in participants exposed to cladribine tablets as compared with participants unexposed to cladribine tablets. Before conducting the final meta-analysis, ORs from countries will be compared visually. If results across countries are obviously heterogeneous, countries with an OR that is obviously different from others will not be included in meta-analysis.

In all of the data sources, to evaluate the potential for bias on the MCA outcome that is related to lack of complete follow-up from birth through 1 year of age, maternal and infant demographics and baseline characteristics will be summarized for comparison between the infants with complete follow-up through age 1 year versus those without complete follow-up through age 1 year.

Data quality assessment

Data quality assessments will be conducted by each participating research institute in the CLEAR study. The following data-related quality indicators will be assessed using the EMA Registry-based Study Guideline,[19] and will be adapted to the study objectives:

- Consistency—the uniformity of core data elements over time (data recording density and frequency over time);
- Accuracy—the extent to which data are entered accurately (i.e., absence of errors, contradictions, value impossibilities, duplicates);
- Completeness—the extent to which data are non-missing; and
- Representativeness—the extent to which the target population is reflected by registry data (for this study representatives will be defined as the extent to which the target population is reflected by the study population).

At the time of the interim analysis and at the final analysis, each country with at least 10 pregnancies of exposed women is anticipated to report on consistency and accuracy indicators, excluding indicators that are addressed by routine data quality checking procedures (as is the case with some indicators in the German MS and Pregnancy Register and the PHS Datasets). Representativeness indicators will be evaluated for each data source at the time of the full interim analysis (if a full interim analysis is triggered and the data source contributes to the analysis), and at the time of the final analysis.

Results

Status update

As of January 2024, a total of 28–36 (data are approximate due to masking of small counts in countries with data sharing restrictions) pregnancies of women exposed to cladribine tablets, and 2834 pregnancies of women who were not exposed, were recorded in the data sources from Denmark, Finland, France, Germany, Scotland,

Table 1. Updated recruitment status (as of January 2024): pregnant women with MS.

	Denmark	Finland	France	Germany	Scotland	Sweden	Total counts
Women exposed to cladribine tablets							
Launch of cladribine tablets	October 9, 2017	November 15, 2017	March 19, 2021	September 15, 2017	September 21, 2017	March 23, 2018	—
Data available for pregnancies of exposed women[a]	No	Yes	Yes	Yes	Yes	Yes	28–36
Number of pregnancies from unexposed women	75	465	NA	248	NA	844	2834
Latest report date[b]	January 3, 2024	December 31, 2022	April 7, 2023	September 30, 2023	December 31, 2023	December 31, 2022	—

Women were exposed to cladribine tablets during pregnancy and/or within 6 months before the start of pregnancy (defined by the last LMP). Pregnancy counts are obtained from annual feasibility checks. Norway is currently in the startup phase and has not yet provided counts. Counts from France are obtained from Vukusic et al.[20]
[a]Due to the low number of pregnancies recorded in some countries the data have been masked and total counts provided as a range.
[b]Dates reflect data lag of each country's register.
LMP, last menstrual period; MS, multiple sclerosis; NA, not available.

and Sweden (Table 1). Currently, the first interim analysis has been conducted using German pregnancy counts. The final analysis has not been performed due to the small number of exposed pregnancies.

Discussion

The CLEAR study is the first post-authorization safety study in MS using multiple national registries in Europe to assess the effect of cladribine tablets on pregnancy and infant outcomes.

While one report has suggested that fingolimod use may be linked to an increased risk of birth defects,[21] there is scant evidence of this for other DMTs. In fact, the majority of existing data on pregnancy and infant outcomes in women with MS exposed to DMTs—both those indicated for MS and those prescribed for off-label use—indicate no relationship between DMT use and adverse pregnancy outcomes.[22–25] Of note, in our maternal cohort unexposed, we included pregnant women who had previously been exposed to methotrexate and rituximab, owing to evidence of increasing off-label use of these DMTs in the Nordic countries.[26–31] That data are available for other DMTs taken during pregnancy in women with MS, and that certain DMTs may be associated with adverse pregnancy outcomes, highlight the need to obtain more real-world evidence on the effects of cladribine tablets in this population.

The strength of the CLEAR study is the inclusion of a large number of data sources to assess the safety of cladribine use during pregnancy in a real-world setting and a first proof of concept using existing data structures to collect relevant postapproval safety data. Despite the inclusion of several data sources across multiple European countries, low numbers of exposed women are expected in the CLEAR study, a major limitation. This is primarily due to the contraindication of cladribine tablets during pregnancy—meaning these are likely unplanned pregnancies or patients not adhering to treatment guidelines—and small population sizes in Nordic countries. While this limits the precision of comparative risk estimates, this provides evidence of the effectiveness of risk minimization measures.

Furthermore, the low number of pregnancy counts in the CLEAR study may be due to the age of the women receiving cladribine tablets. Recent data show that the mean age of initiation of cladribine tablets under standard of care is 41 years (±SD: 12.6 years)[32]; therefore, many women may have already had their desired number of children by the time of treatment initiation, resulting in low pregnancy counts. It is worth noting, however, both the large standard deviation of 12.6 years, which encompasses women in their late 20s and 30s, and the global rise in pregnancy in women in their late 30s and beyond.[33] Pregnancies where the woman or the man were

exposed to cladribine tablets may also have been missed—resulting in low pregnancy counts—as evidence of drug utilization for cladribine tablets in real-world data (RWD) sources was difficult to predict at the time of approval. Additionally, in certain countries, garnering permission to use patient data in registry-based studies can result in low pregnancy counts; however, in Norway, the challenge is for sufficient numbers of neurologists to deliver the patient data.

One of the strengths of CLEAR, which aims to address the limitation of low pregnancy counts, is the use of RWD sources. Prospective, treatment-specific registries and targeted studies are typically used to obtain pregnancy outcome data in women with MS; however, these studies often have small sample sizes due to challenges recruiting pregnancies; long study periods; and selection bias.[34] CLEAR, on the other hand, extracts data from existing disease-specific registries and national databases, ensuring a high coverage of the target population, and maximizing the likelihood of identifying exposed women. This approach to gathering data is also intended to improve the quality and robustness of the outcome data.[34]

However, timeliness of Nordic registries is a challenge for pregnancy studies of new drugs that are contraindicated. These data sources are characterized by long lag times from the data cut-off dates to the reporting of the results, due to two intrinsic components: time needed to record the information; and time taken to make the register data available for research. This leads to obtaining pregnancy counts in women with MS exposed to cladribine tablets with 2 years lag in Finland and with 1 year lag in Sweden. From the data sources included in the study, the MBRs have the longest lag time (12–16 months), because some variables are not completed until 12 months after the birth (e.g., MCAs). The time lag of the MBR will also influence the availability of study outcomes and reduce the number of pregnancies included in the analysis.

The staggered methodological approach used in CLEAR is also a key advantage when handling potentially low pregnancy counts. Rather than performing an analysis for each country, analysis is triggered by overall pregnancy counts. This prevents unnecessary and costly data analyses, particularly in Nordic countries where the acquisition of individual level data is a lengthy process.

In addition, CLEAR uses a DMT-unexposed internal comparator from the same population as the exposed (pregnant women with MS/pregnancies with a father with MS). The use of a disease comparator ensures high internal validity of the estimate calculated for women with MS taking cladribine tablets; whilst linked population-based data allow for the linkage of data between mother—and father where paternal data are available—and offspring. The linkage of paternal and offspring data is another novel aspect of the CLEAR study and may allow for the analysis of pregnancy outcomes where fathers are exposed to cladribine tablets. Historically, these data have been difficult to obtain, as paternity can be difficult to confirm in a database setting and/or paternal data may not be linked to the offspring.

One of the aims of CLEAR is to assess the effects of paternal exposure to cladribine tablets on pregnancy outcomes. However, the number of pregnancies fathered by men with MS is expected to be small due to the cladribine tablet label and strong female-male ratio in MS, so sample sizes were not calculated. Furthermore, data on fathers are not available for all countries. In Finland, Norway, and Sweden, information from fathers can be obtained from the population register for children whose parents are married or, in the case of an unmarried couple, if the fatherhood has been confirmed through a legal process. However, cohorts of fathers with MS will not be included in Germany and France because the German MS and Pregnancy Register and the French RESPONSE registry only include pregnant women with MS. The cohort of fathers will also not be included in Scotland, as it requires a specific study consent. Owing to this country-specific variation in the reporting of paternal data, the expected low counts for this population, and the high costs associated with paternal linkage, interim reports will not include paternal data and linkage will only be performed once for the final report.

Due to data privacy rules, some countries cannot report observations specifying nonzero counts in cases where counts are <5, these are subsequently masked in result outputs. Small sample sizes and rare outcomes are expected to pose challenges, such as limiting the estimation of the prevalence of study outcomes, performing comparative analyses,

and pooling estimates in the meta-analysis. In addition, multifetal gestations are expected to induce statistical dependencies.

One advantage of the CLEAR study design is the quality of the data sources included. In particular, many of the data sources provide detailed information and follow-up data on both mothers and infants, enabling a broader insight into both pregnancy and longer-term infant outcomes. In turn, this helps to provide a more comprehensive picture of pregnancy in this population.

Country-specific data confounders are another key limitation of CLEAR. In particular, there are country-specific discrepancies in the reporting of alcohol consumption, drug abuse, family history, maternal exposure to folic acid, and the number of previous abortions. This variation can affect the validity of between country comparisons. However, the use of data quality indicators should help with understanding the level of data quality and consistency across participating data sources, and aid in the identification of data issues.

Each country also presents its own unique set of limitations, impacting both the internal and external validity of the data reported. The internal validity may be impacted by both the German and Nordic registries. For example, the voluntary registration for the German registry may potentially result in selection bias, and the registries used in the Nordic countries may impact internal validity as they report dates for drug prescription fills (rather than the dates treatment was received), may not include data for medicines administered in the hospital, and may be missing data for SAs and terminations. However, the effects of these factors are expected to be negligible. The lack of representativeness may also impact the generalizability of the results, and therefore impact the external validity.

Conclusion

The CLEAR study has robustly followed patient counts yearly and elucidates accumulated pregnancies with women exposed to cladribine tablets since launch. Although low pregnancy counts are anticipated, the use of population-based national data sources and pregnancy and MS registries will help to identify rare cases of unintended exposure to cladribine tablets during pregnancy, and provide a better insight into pregnancy and infant safety outcomes with minimal loss to follow-up. CLEAR is a novel and unique approach which uses existing registries to conduct post-authorization safety studies required by the medication regulatory agencies. If shown to be successful, other studies can consider similar approaches to accelerate and facilitate research in this field.

Declarations

Ethics approval and consent to participate

Ethical approvals vary by country and are summarized below: Denmark: approval from Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) is not required because the study is registry-based. Finland: no ethical approval is required for registry-based studies. Preliminary monitoring of exposed pregnancies is conducted as a part of the "Drugs and Pregnancy" project. Institutional Review Board approved the project and waived the requirement for obtaining informed consent for the secondary use of health administrative data from study participants (THL/2104/6.02.00/2017 and THL/5875/6.02.00/2022). An application will be submitted for specific data linkages for the full study. France: no ethical approval is required for the CLEAR study. Data used in this manuscript has been obtained from a publication.[20] Germany: The registry is IRB-approved. The IRB has been notified about the use of registry data for CLEAR. No additional ethical reviews and approvals are required. Norway: approval for the full study is obtained from the Regional Committees for Medical and Health Research Ethics (REK, project ref. #2023-570520). Sweden: no ethical approval is required for aggregated statistics (monitoring counts). An application for ethics approval for the use of individual level data will be submitted individual-level data linkages for the full study. Scotland: no ethical approval is required. Data permit application is required. As this is a non-interventional study using pseudonymized secondary data, and the study involves no risk or potential harm to the study patients. No specific informed consent from patients is required for participation in this study. In Norway and in Sweden, the patients sign an informed consent before providing data to the MS Registry and Biobank. Furthermore, in Germany and France, participants give written or oral witnessed

consent to participate in the MS pregnancy registry and the RESPONSE Registry, respectively.

Consent for publication
Not applicable.

Author contributions
Kerstin Hellwig: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

Melinda Magyari: Conceptualization; Data curation; Investigation; Methodology; Visualization; Writing – review & editing.

Thomas M. MacDonald: Conceptualization; Data curation; Investigation; Methodology; Writing – review & editing.

Carolyn E. Cesta: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

Stig Wergeland: Investigation; Visualization; Writing – review & editing.

Maarit K. Leinonen: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

Asher Ornoy: Conceptualization; Investigation; Methodology; Visualization; Writing – review & editing.

Sandra Vukusic: Data curation; Investigation; Visualization; Writing – review & editing.

Alexandra Lauer: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

Xiaolei Zhou: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

Alison Kawai: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

Rachel Weinrib: Conceptualization; Investigation; Methodology; Visualization; Writing – review & editing.

Alejandro Arana: Conceptualization; Investigation; Methodology; Visualization; Writing – review & editing.

Tahani Boumenna: Conceptualization; Formal analysis; Investigation; Methodology; Visualization; Writing – review & editing.

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Availability of data and materials

Not applicable.

ORCID iDs

Kerstin Hellwig https://orcid.org/0000-0003-4467-9011

Melinda Magyari https://orcid.org/0000-0002-0972-5222

Supplemental material

Supplemental material for this article is available online.

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Appendix

Abbreviations

CI	confidence interval
CPP	Comité de Protection des Personnes
DMT	disease-modifying therapy
DNA	deoxyribonucleic acid
EMA	European Medicines Agency

EUROCAT	European Surveillance of Congenital Anomalies	OR	odds ratio
FDA	Food and Drug Administration	PHS	Public Health Scotland
IEC	Independent Ethics Committee	PIN	personal identification number
IRB	Institutional Review Board	Q	quartile
LMP	last menstrual period	REK	Regional Committees for Medical and Health Research Ethics
MBR	Medical Birth Register		
MCA	major congenital anomalies	RWD	real-world data
MS	multiple sclerosis	SA	spontaneous abortion
NRS	National Record of Scotland	SB	stillbirth
OFSEP	*Observatoire Français de la Sclérose en Plaques*	SD	standard deviation
		T	trimester