Non-Interventional Study Protocol

Study protocol number	MS 700568-0002
Title	Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine − CLARION
Protocol version identifier	V. 1.0
Protocol date/version	19 June 2018/ Version 1.9
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Active substance	Cladribine
Medicinal product	Mavenclad®
Product reference	EMEA/H/C/004230
Procedure number	EMEA/H/C/004230/MEA/PRO/002
Marketing authorisation holder	Merck Serono Europe Limited 56 Marsh Wall London E14 9TP United Kingdom
Joint PASS	No
Research question and objectives	The research question is: What is the safety profile in terms of adverse events of special interest ([AESI]: severe infections, herpes zoster infection, tuberculosis, progressive multifocal leukoencephalopathy (PML), other opportunistic infections, and malignancies) in patients with highly active

multiple sclerosis (MS) newly initiating oral cladribine in the routine clinical practice, and how is this profile comparatively to the safety profile of highly active MS patients newly initiating oral fingolimod?

Primary objective:

- To further characterize and compare the risk, in terms of incidence of AESI (severe infections, herpes zoster infection, tuberculosis, PML, other opportunistic infections, and malignancies) in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod.

Secondary objectives:

- To assess the impact of the prior use of immunomodulatory / immunosuppressive agents on the incidence of AESI in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod;
- To characterize the incidence and duration of severe lymphopenia in patients with highly active R(R)MS newly initiating oral cladribine;
- To describe further disease modifying therapy (DMT) prescribed when disease activity recurs in patients with highly active R(R)MS newly initiating oral cladribine;

Exploratory objectives:

- To characterize treatment discontinuation and the reasons for discontinuation in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod;
- To further characterize the relationship between severe lymphopenia and AESI in patients with highly active R(R)MS newly initiating oral cladribine.

Countries of study: Australia, Belgium, Czech Republic, Denmark, Finland, France, Germany, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland, Turkey, and United Kingdom (UK)

Author: PPD

Merck KGaA
Frankfurter Strasse 250
64293 Darmstadt, Germany

– Confidential –

Marketing authorization holder

Marketing authorisation holder (MAH)	Merck KGaA Frankfurter Strasse 250 64293 Darmstadt, Germany
MAH contact person	PPD Merck KGaA Frankfurter Str. 250 64293 Darmstadt, Germany

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2 List of Abbreviations

AE	Adverse event
AESI	Adverse event of special interest
AR	Adverse reaction
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CNS	Central nervous system
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
DMT	Disease-modifying therapy
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
HCP	Health care provider
HPV	Human papillomavirus
IM	Immunomodulatory
IMSE	Immunomodulation and Multiple Sclerosis Epidemiology Study
IRB	Institutional Review Board
IS	Immunosuppressive
LLN	Lower limit normal
MAH	Marketing Authorization Holder
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSBase	Multiple Sclerosis dataBase
MSDS 3D	Multiple Sclerosis Management System 3D
NMSC	Non-melanoma skin cancer

NTD	NeuroTransData
OFSEP	Observatoire Français de la Sclérose en Plaques
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PHs	Proportional hazards
PID	Personal Identity Number
PML	Progressive Multifocal Leukoencephalopathy
PRAC	Pharmacovigilance Risk Assessment Committee
PY	Person-years
RR	Relative risk
RRMS	Relapsing-remitting multiple sclerosis
RMS	Relapsing multiple sclerosis
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SSC	Study Steering Committee
SmPC	Summary of Product Characteristics
SID	Study Identification Number
UK	United Kingdom

3 Responsible Parties

Responsible parties	Contact details
Principal lead investigator	PPD

3.1 Responsibilities of the Participating Registry/Database

The participating registry/database representative is responsible for the conduct of the study. The participating registry/database representative will ensure that the study is performed in accordance with the protocol and will ensure the quality and integrity of data, following all applicable international and national guidelines.

This non-interventional study will not interfere with treatment prescription by physicians. Accordingly, the physician will decide in advance the best therapeutic strategy for each patient according to current practice, regardless of the potential participation of this patient in the study.

3.2 Study Steering Committee

A Study Steering Committee (SSC) has been established and a Study Steering Committee Charter will be in place that describes the SSC roles and responsibilities.

The SSC composition should provide a good balance of expertise, by including experts from neurology, oncology, infectious diseases, epidemiology, patient representatives, who, collectively, have the scientific, medical, patient perspective, and study management experience to design and conduct the study, and evaluate the study results appropriately. Study sponsor's representatives, selected based on their expertise, will also participate to SSC meetings as invited observers.

The SSC provides scientific advice and guidance with regard to the study methodology (design, data collection and analysis), including with respect to protocol revision and amendments, as well as clinical input aspects of the study.

The SSC is responsible for overseeing the conduct of the study and making recommendations if needed, discussing study results and communication plan and motivating physicians from the registries/ databases participating to the study.

4 Abstract

Title	Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine − CLARION Protocol date: 19 June 2018/ Version 1.9 Protocol author: PPD Merck KGaA
Rationale and background	In clinical studies, approximately 20% to 25% of the subjects treated with oral cladribine 3.5 mg/kg as monotherapy developed transient Grade ≥ 3 lymphopenia. Reduction of lymphocytes is a pharmacological action of cladribine and part of its mechanism of action in multiple sclerosis (MS). Lymphopenia is an expected event and severe lymphopenia has been defined as an important identified risk for cladribine. Apart from herpes zoster, there was no increased risk of infections including severe infections or opportunistic infections in patients receiving oral cladribine in the clinical dataset. However, as cladribine affects the immune system, severe infections and opportunistic infections (including progressive multifocal leukoencephalopathy [PML]) have been defined as important potential risks, and herpes zoster infection and tuberculosis as important identified risks. In addition, malignancies are considered as an important potential risk; the possibility of an increased risk of developing malignancies with oral cladribine, which can occur a long time after drug exposure, remains uncertain. For this reason, the Committee for Medicinal Products for Human Use (CHMP) requested the Applicant to conduct a study to assess the potential of an increased risk of developing malignancies through a comparative post-authorization safety study (PASS). Fingolimod has been selected as the comparator for this study given that both cladribine and fingolimod have oral administration and target a similar indication, thereby minimizing possible indication bias and selection bias. Similar to oral cladribine, the core pharmacodynamic effect of fingolimod is a dose-dependent reduction of the peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. Furthermore, fingolimod is widely used, which will facilitate patient recruitment. Overall, the safety of oral cladribine should be monitored for a period extending beyond pharmacological exposure, warranting a long-term study period, specifically needed to further assess the potential risk of malignancy. Therefore, this prospective, observational cohort study will follow a total of 8,000 patients newly initiating cladribine or fingolimod (ratio 1:1) for a period of 10 years, thus allowing the detection of low-

	frequency and late-onset events that cannot be adequately detected during Phase III clinical development. This PASS is part of the Risk Management Plan (RMP) as an additional pharmacovigilance activity to further characterize the safety profile of oral cladribine tablets, in particular in terms of incidence of adverse events of special interest (AESI), in a real-world setting.
Research question and objectives	The research question is: What is the safety profile in terms of AESI (severe infections, herpes zoster infection, tuberculosis, progressive multifocal leukoencephalopathy (PML), other opportunistic infections, and malignancies) in patients with highly active MS newly initiating oral cladribine in the routine clinical practice, and how is this profile comparatively to the safety profile of highly active MS patients newly initiating oral fingolimod? Primary Objective: • To further characterize and compare the risk, in terms of incidence of AESI (severe infections, herpes zoster infection, tuberculosis, PML, other opportunistic infections, and malignancies) in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod. Secondary Objectives: • To assess the impact of the prior use of immunomodulatory / immunosuppressive agents on the incidence of AESI in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod; • To characterize the incidence and duration of severe lymphopenia in patients with highly active R(R)MS newly initiating oral cladribine; • To describe further disease modifying therapy (DMT) prescribed when disease activity recurs in patients with highly active R(R)MS newly initiating oral cladribine; Exploratory Objectives: • To characterize treatment discontinuation and the reasons for discontinuation in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod; • To further characterize the relationship between severe lymphopenia and AESI in patients with highly active R(R)MS newly initiating oral cladribine;

Study Design	This PASS is a multi-country, multi-center, long-term, prospective, observational study evaluating the safety in patients with highly active R(R)MS newly initiating oral cladribine (cladribine cohort) as compared to R(R)MS patients newly initiating fingolimod (comparator cohort). The study is projected to last for a maximum of 15 years, with a maximum 5-year recruitment period until both cohorts have reached 4,000 patients and with a follow-up of 10 years for each patient. The study is based on secondary use of data in certain countries and a mixed model, with both secondary use of data and additional primary data collection in other countries. In the countries with the mixed model, existing data sources (MS registries or national registers) will be supplemented by additional data collection by adding modules to facilitate the collection of the variables needed specifically for the study, variables which are not routinely collected and then readily available in the selected data sources. For each patient, data collection will begin after the signature of the informed consent form – noting that patient consent applies to all countries in which additional primary data collection will be conducted and to some countries where secondary use of data will be performed – and continue during 10 years, as each patient will be followed-up for a period of 10 years, except if s/he is lost to follow-up, or withdrawn his/her consent, or die before the end of the follow-up period. Follow-up will continue regardless of oral cladribine or fingolimod discontinuation.
Population	For inclusion of a patient in the study, <u>all</u> of the following inclusion criteria must be fulfilled: • Newly initiating oral cladribine or fingolimod according to the local label for MS, • Written informed consent obtained (in all countries for which the mixed model (secondary data supplemented with primary data) applies and in some countries where only secondary data is used). Patients are not eligible for this study if they fulfill <u>any</u> of the following exclusion criteria: • Received fingolimod prior to initiating oral cladribine, • Received oral cladribine prior to initiating fingolimod.
Outcomes	Primary outcomes (on cohort level): • Number of AESIs (severe infections, herpes zoster infection, tuberculosis, PML, other opportunistic infections, and

	malignancies) in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod. Secondary outcomes (on cohort level): • Number of AESIs in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod by prior use of immunomodulatory/ immunosuppressive agents; • Number and duration of severe lymphopenia events in patients with highly active R(R)MS newly initiating oral cladribine; • Number of patients by DMT (immunosuppressive or immunomodulatory agents) after oral cladribine treatment in patients who experience a recurrence of the disease activity in patients with highly active R(R)MS newly initiating oral cladribine. Exploratory outcomes (on cohort level): • Number of patients discontinuing treatment, overall and by reasons for discontinuation in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod; • Number and time points of severe lymphopenia and AESI in patients with highly active R(R)MS newly initiating oral cladribine.
Variables	At enrolment (corresponding to the date of oral cladribine or fingolimod treatment initiation): • Demographics • Disease history: • date of diagnosis of MS • date of onset of MS, if available disease clinical course at enrolment • Expanded Disability Status Scale (EDSS) score closest to enrolment • number of relapses within one year prior to enrolment • medical history, including malignancies, severe and opportunistic infections During follow-up: • date and reasons for discontinuation of oral cladribine and fingolimod treatments, when relevant • DMT: generic or trade names, doses, as well as the starting and discontinuation dates, with reasons for start/ discontinuation

	• concomitant medications, including immunosuppressive/ immunomodulatory agents (other than DMTs) such as corticosteroid treatment • Date of death, if applicable Specific risk factors for the outcomes of interest: At enrolment: • prior DMT use • prior immunomodulatory or immunosuppressive agents (other than DMTs; e.g., chemotherapeutic agents, corticosteroids for systemic use, other immunosuppressive) taken within 28 days before enrolment • alcohol consumption and smoking • obesity • infection status (e.g. human papillomavirus [HPV] status and other infections) and vaccines • any personal and family history of malignancy During follow-up with their respective dates: • infection status • use of female hormones • IS / IM therapy • radiation exposure • alcohol consumption • smoking • obesity
Data Sources	Data will be collected by the treating physicians at routine visits of the patients. The following data sources will be used to collect the data needed for the study purpose: • Observatoire Français de la Sclérose en Plaques (OFSEP; France), • NeuroTransData database (NTD; Germany), • Multiple sclerosis management system 3D (MSDS 3D; Germany, Spain and Switzerland), • Italian MS Registry (Italy),

	• Multiple Sclerosis dataBase (MSBase; Australia, Belgium, Czech Republic, Italy, the Netherlands, Spain, Switzerland, Turkey, UK), • The national healthcare and MS registers in the Nordic countries (Denmark, Finland, Norway and Sweden).
Study Size	The study aims to enroll 8,000 patients (4,000 patients per cohort) from centers specialized in the management and treatment of MS patients in Europe and other participating countries launched (Australia, Turkey).
Data Analysis	In the primary analysis, using the intention-to-treat exposure definition, the crude and adjusted incidence rates of the different AESIs along with 95% CIs will be estimated in both oral cladribine patients and fingolimod patients. To compare the adjusted incidence of AESI between oral cladribine and fingolimod patients, the incidence rates ratios of the AESI together with the 95% CIs will be estimated by Poisson regression models adjusted for the key prognostic factors (including prior use of immunomodulatory/ immunosuppressive agents). The impact of the prior use of immunomodulatory/ immunosuppressive agents on the incidence of AESI in patients initiating oral cladribine or fingolimod will be assessed by stratifying the analyses and by subgroup analyses. In the secondary analyses, the crude and adjusted incidence rate of severe lymphopenia among oral cladribine patients as well as the 95% CI will be estimated using Poisson regression models. As for the primary analysis, the adjustments will be done for the key prognostic factors and results displayed by means of forest plots. Analysis of duration of severe lymphopenia will be descriptive. For the primary and secondary analyses, sensitivity analyses will be performed: • considering an induction period of 6 and 12 months after treatment initiation for the analyses regarding malignancies; • using time since last dose exposure definition instead of ITT exposure. • considering an on-treatment analysis in which the ITT exposure definition is used but patients' follow-up will be censored 6 months (or 12 months) after oral cladribine or fingolimod treatment discontinuation;

	• as an alternative to the parametric Poisson regression, the cumulative incidence of AESIs during follow-up in both cohorts will be described non-parametrically. • potential imbalance in the baseline characteristics (assessed at enrolment) between the 2 cohorts (oral cladribine and fingolimod) will corrected for using propensity score adjustment will be considered.
Milestones	Protocol approved by the Pharmacovigilance Risk Assessment Committee (PRAC): estimated for Q2 2018 Registration in the EU PAS register: 1 month at the latest after PRAC approval of the protocol Anticipated dates of cladribine launch in planned participating countries: from Q3 2017 to Q2 2019 (depending on market access conditions) Institutional Review Board (IRB) approvals by country, according to national regulations: up to 9 months after protocol approval (anticipated date for the first approvals in Q3 2018) Start of data collection: as soon as possible after all necessary approvals have been received in a specific country (anticipated start dates for the first countries in Q3 2018) End of data collection: 15 years after start of data collection (anticipated in Q3 2033) First interim report: 3 years after start of data collection (anticipated in Q3 2021), with data collected over the first 2 years Second interim report: 6 years after start of data collection (anticipated in Q3 2024), with data collected over the 5-year period anticipated for patient recruitment Third interim report: 9 years after start of data collection (anticipated in Q3 2027) Fourth interim report: 12 years after start of data collection (anticipated in Q3 2030) Final report of study results: anticipated in Q3 2034, at the latest 1 year after the end of data collection In addition, study progress updates presenting the course of enrolment along with safety data from the pharmacovigilance database will be submitted with each Periodic Benefit-Risk Evaluation Report (PBRER)

5 Amendments and Updates

None.

6 Milestones

Milestone	Planned date
Protocol approved by the PRAC	Q2 2018
Registration in the EU PAS register	1 month at the latest after PRAC approval of the protocol
Anticipated dates of launch in planned participating countries	**From Q3 2017 to Q4 2019 (depending on market access conditions):** • Germany, UK: Q3 2017 • Denmark, Norway: Q4 2017 • Spain, Sweden, The Netherlands: Q1 2018 • Australia: Q2 2018 • Belgium, Finland, France: Q3 2018 • Czech Republic, Italy, Switzerland: Q4 2018 • Turkey: Q2 2019
Institutional review board (IRB) approvals by country, according to national regulations	Up to 9 months after protocol approval (anticipated dates for the first approvals in Q3 2018)
Start of data collection	As soon as possible after all necessary approvals have been received in a specific country (anticipated start dates for the first countries in Q3 2018)
End of data collection	15 years after start of the data collection (anticipated in Q3 2033)
First interim report	3 years after start of data collection (anticipated in Q3 2021), with data collected over the first 2 years
Second interim report	6 years after start of data collection (anticipated in Q3 2024), with data collected over the 5-year period anticipated for patient recruitment
Third interim report	9 years after start of data collection (anticipated in Q3 2027)
Fourth interim report	12 years after start of data collection (anticipated in Q3 2030)
Final report of study results	Anticipated in Q3 2034, at the latest 1 year after the end of data collection
Study progress updates	To be submitted according to periodicity of each PBRER

7 Rationale and Background

Epidemiology of Multiple Sclerosis

Multiple sclerosis (MS) is an immune-mediated, chronic inflammatory disease of the central nervous system (CNS) characterized by the demyelination and destruction of axons (Tullman, 2013). With no definite cause established, MS has been hypothesized to result from a complex interaction between individual genetic susceptibility and environmental factors that act as triggers of a self-sustained auto-immune response (Noseworthy, 2000). With a peak of onset averaging at the age of 30 years in both genders, MS occurs predominantly in women with a female:male ratio of 3:1 (Kingwell, 2013).

Globally, the median estimated prevalence of MS is 33 patients per 100,000 population. MS median estimated prevalence varies substantially across regions, with North America and Europe presenting the highest prevalence (140 and 108 patients per 100,000 population, respectively) (Multiple Sclerosis International Federation, 2013). Within Europe, the prevalence is highest in Denmark (227 MS patients per 100,000 population), and Sweden (189 MS patients per 100,000 population), while in most of the other countries the prevalence is under 100 MS patients per 100,000 population (Multiple Sclerosis International Federation, 2013).

Regarding incidence, globally, the median estimated incidence of MS is 2.5 per 100,000 person-years (PY) (Dua, 2008). Regionally, the median estimated incidence is greatest in Europe (3.8 per 100,000 PY) (Dua, 2008). European countries with highest incidence of MS are Bosnia and Herzegovina (12 per 100,000 PY), Latvia (11.6 per 100,000 PY), Czech Republic (11 per 100,000 PY), and Estonia, Hungary and Iceland (each at 10 per 100,000 PY) (Multiple Sclerosis International Federation, 2013).

Studies indicate that MS patients show a nearly 3-fold increase in mortality relative to the general population, and about half of them are attributed to MS as the underlying cause of death (Scalfari, 2013).

Clinical presentation and categorization of MS

MS is not characterized by a singular, well-defined clinical presentation common to all MS patients. The symptoms, which include a combination of cognitive, sensory and motor manifestations, vary among patients and throughout the disease course according to the CNS areas affected and the severity of the demyelinating attacks.

Approximately 85% of patients with MS have initially a relapsing-remitting form of MS (RRMS) (Multiple Sclerosis International Federation, 2013), which is characterized by alternating periodic acute exacerbations of disease activity (relapses) and periods of remission, consisting of partial or complete recovery (Lublin, 2014).

The most important features of highly active R(R)MS include frequent relapses with incomplete recovery, and/or high radiological burden of disease, rapid accrual of disability after disease onset, with otherwise typical features of RRMS (Lublin, 2014). Data on the epidemiology of highly active

RRMS is lacking and currently the proportion of patients that are classified as highly active comes from clinical trials. However, data show that around 14.4% to 14.8% of patients who had experienced breakthrough disease activity (≥1 relapse in the 12 months prior to randomization) (Gold, 2013; Rudick, 2006) and 22.2% of treatment-naïve patients (Polman, 2006) met the criteria for highly active RRMS (≥2 relapses in the year prior to study entry and ≥1 Gd+ lesion on T1-weighted magnetic resonance imaging [MRI] at study entry) (Gold, 2013; Rudick, 2006; Polman, 2006).

Treatment and management of MS

Treatment options include disease-modifying therapies, medications used to treat relapses and exacerbations, as well as symptomatic treatments. Disease-modifying therapies (DMTs) aim to reduce frequency and severity of relapses or slow progression (ie, modify the course of the disease).

Currently, the 'first-line' DMTs (interferon beta or glatiramer acetate) are chosen as initial therapies for the majority of patients with MS. However, if the effect of the initial treatment shows to be unsatisfactory, the patient might escalate treatment and switch to second-line drugs, such as natalizumab and fingolimod. These drugs have more potent anti-inflammatory, immunoregulatory or immunosuppressive properties, but also have the disadvantage of more serious side effects than the first-line drugs (Scolding, 2015), such as progressive multifocal leukoencephalopathy (PML).

Oral Cladribine

Three clinical trials for oral cladribine have been completed (CLARITY EXT, ORACLE MS and ONWARD), and data from these trials (Leist, 2014; Montalban, 2016), as well as extension phase of the CLARITY trial (Giovannoni, 2013) and the interim long-term follow-up data from a prospective registry (the PREMIERE registry), have provided information on the efficacy and safety of oral cladribine. In total, the follow-up consisted of >10,000 PY of exposure for both oral cladribine and placebo, with over 8 years of follow-up for some patients.

In the CLARITY trial (Giovannoni, 2010), patients with active RRMS were randomized to placebo or cladribine tablets (3.5 or 5.25 mg/kg body weight) for 2 years; each dose showed significant benefits in rate of relapse, disability progression, and MRI measures. Cladribine treatment in CLARITY produced efficacy improvements that were maintained in patients treated with placebo in the extension phase (Giovannoni, 2013).

Approximately 20% to 25% of the patients treated with 3.5 mg/kg as monotherapy developed transient Grade ≥ 3 lymphopenia. Grade 4 lymphopenia was observed in 0.7% of patients. Overall, nearly 90% of patients recovered by the end of the trials. The remaining patients recovered during long-term follow-up without developing severe or opportunistic infections.

Herpes zoster infection is considered as an important identified risk of cladribine treatment. The observed incidence rates in the monotherapy oral cohort for herpes zoster infection were 0.86 adjusted adverse events (AEs) per 100 PY for oral cladribine 3.5 mg/kg vs. 0.20 for placebo, and for severe herpes zoster infection 0.9 vs. 0.5, respectively. The incidence of herpes zoster infection was higher during periods of Grade 3 or 4 lymphopenia compared to the time when the patients were not experiencing Grade 3 or 4 lymphopenia.

Incidence rates of the most common infections, including the most common severe infections, were similar between the placebo and the oral cladribine exposed groups, with the exception of herpes zoster infection as described above. The incidence rates for infections, in general, were 24.93 vs. 27.05 adjusted AEs per 100 PY (cladribine 3.5 mg/kg monotherapy vs. placebo), and for severe infections 0.84 vs. 0.86, respectively. There was no evidence for an increased risk of opportunistic infections in subjects treated with oral cladribine (incidence rates were 1.08 and 1.17 for oral cladribine 3.5 mg/kg monotherapy and placebo, respectively). However, tuberculosis has been defined as an important identified risk, with overall 3 cases observed in the cladribine development program. All cases were reported prior to the implementation of mandatory pre- screening for tuberculosis; no cases occurred thereafter.

The types of malignancies reported in the oral cladribine clinical program were in line with what is reported in the general population and in patients with MS. No malignancy pattern reflective of immunosuppression was observed, and no malignancies were seen in cell types most affected by cladribine (eg, lymphomas). There is no evidence of a dose effect of oral cladribine on malignancy occurrence and with cladribine, there was no change in the risk of malignancy over time. The overall malignancy rate with cladribine was similar to the rates observed with other DMTs approved in MS. In summary, there is no conclusive evidence for an increased risk of malignancy with oral cladribine compared to placebo with a risk difference of 0.2033 per 100 PY (95% confidence interval [CI]: -0.0785, 0.3947) in the overall exposed cohort. An independent meta-analysis of study results from Phase III trials of DMTs used in RRMS (Pakpoor, 2015) showed that the malignancy risk profile of cladrbine in the CLARITY study was comparable to that observed in similar trials with other DMTs.

Fingolimod

Fingolimod (Gilenya) is an orally available DMT currently approved in the European Union (EU) and in Australia for the treatment of highly active RRMS in the following patient groups: 1) patients with highly active disease despite a full and adequate course of treatment with at least 1 DMT; or 2) patients with rapidly evolving severe RRMS defined by 2 or more disabling relapses in 1 year, and with 1 or more Gadolinium enhancing lesions on a brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI (European Medicines Agency, 2011).

Side effects commonly found in patients treated with fingolimod during clinical trials with an observation period of 1 (Cohen et al., 2010), or 2 years (Kappos et al., 2010) include dose-dependent, self-limited bradycardia and atrioventricular conduction block, macular edema, mild arterial hypertension, self-limited liver enzyme elevation and skin cancer. Higher doses of fingolimod (1.25 mg) than the approved 0.5 mg dose were associated with higher frequency of lower respiratory tract infections (Kappos et al., 2010).

Regarding infections and infestations listed in the Summary of Product Characteristics (SmPC) of fingolimod (European Medicines Agency, 2016), influenza and sinusitis are considered very common; herpes viral infections, bronchitis, tinea versicolor are considered common; pneumonia is considered uncommon and PML and cryptococcal infections have an unknown frequency. Regarding malignant neoplasms, basal cell carcinoma is listed as common and lymphoma as rare during an observation period up to 2 years. Regarding blood and lymphatic system disorders,

lymphopenia is listed as common. Frequencies were defined using the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data).

Fingolimod is notably contraindicated in patients with increased risk for opportunistic infections, severe active infections and known active malignancies (European Medicines Agency, 2016).

Study Rationale

According to current guidelines (EMEA Guideline on Risk Management Systems for Medicinal Products for Human Use [EMEA/CHMP/96268/2005]), marketing authorization holders should consider the implementation of further pharmacovigilance activities when routine pharmacovigilance is likely to be insufficient, especially for the estimation of incidence rate of very rare events (occurring in less than 1 per 10,000 patients) and long-term safety data. In this context, the events that may have a long induction and latency period, such as cancer, may appear years after exposure to oral cladribine and not be reported spontaneously.

Data from clinical trials showed that oral cladribine causes sustained and dose-related lymphopenia. Reduction of lymphocytes is a pharmacological action of cladribine and part of its mechanism of action in MS. Lymphopenia is an expected event and severe lymphopenia has been defined as an important identified risk for cladribine. Apart from herpes zoster, there was no increased risk of infections including severe infections or opportunistic infections in patients receiving oral cladribine in the clinical dataset. As cladribine affects the immune system, severe infections and opportunistic infections (including PML) have been defined as important potential risks, and herpes zoster and tuberculosis as important identified risks.

In addition, other delayed health effects, including the possibility of an increased risk of developing malignancies remains uncertain. As a consequence, the CHMP has requested the Applicant to conduct a study to assess the potential of an increased risk of developing malignancies through a comparative post-authorization safety study (PASS).

Fingolimod has been selected as a comparator given that both fingolimod and cladribine have oral administration and target a similar indication. Therefore, possible indication bias and selection bias are minimized. Similar to oral cladribine, the core pharmacodynamic effect of fingolimod is a dose-dependent reduction of the peripheral lymphocyte count to 20-30% of baseline values. This is due to the reversible sequestration of lymphocytes in lymphoid tissues. Furthermore, fingolimod is widely used, which will facilitate patient recruitment.

This PASS aims to further evaluate the safety profile, including long-term safety aspects, of oral cladribine tablets in patients with highly active MS who are newly initiating this drug under a real-world post-marketing setting, as compared to patients with highly active MS who are newly initiating fingolimod. The study has a focus on measuring the occurrence of adverse events of special interest (AESI), defined as severe infections, herpes zoster infection, tuberculosis, PML, other opportunistic infections, and malignancies.

Therefore, this prospective, observational cohort study will follow-up 8,000 patients in total for an extended period of 10 years, thus allowing the detection of low-frequency and late-onset events

that were detected with difficulty during Phase III clinical development. This PASS is part of the Risk Management Plan (RMP) as an additional pharmacovigilance activity to further characterize the safety profile of oral cladribine in a real-world setting. In addition, data generated through this PASS will be used to measure the effectiveness of some risk minimization measures in line with what is specified in the RMP.

8 Research Question and Objectives

The research questions is:

What is the safety profile in terms of AESI (severe infections, herpes zoster infection, tuberculosis, PML, other opportunistic infections, and malignancies) in patients with highly active MS newly initiating oral cladribine in the routine clinical practice, and how is this profile comparatively to the safety profile of highly active MS patients newly initiating oral fingolimod?

8.1 Primary Objective

- To further characterize and compare the risk, in terms of incidence of AESI (severe infections, herpes zoster infection, tuberculosis, PML, other opportunistic infections, and malignancies) in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod.

8.2 Secondary Objectives

- To assess the impact of the prior use of immunomodulatory / immunosuppressive agents on the incidence of AESI in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod;
- To characterize the incidence and duration of severe lymphopenia in patients with highly active R(R)MS newly initiating oral cladribine;
- To describe further DMT prescribed when disease activity recurs in patients with highly active R(R)MS newly initiating oral cladribine;

8.3 Exploratory Objectives

Exploratory objectives reflect outcomes that might have low completeness or heterogeneity of data collection in participating registries and data sources:

- To characterize treatment discontinuation and the reasons for discontinuation in patients with highly active R(R)MS who are newly initiating oral cladribine or fingolimod;
- To further characterize the relationship between severe lymphopenia and AESI in patients with highly active R(R)MS newly initiating oral cladribine.

9 Research Methods

9.1 Study Design

9.1.1 Design Overview

The PASS is a multi-country, multi-center, long-term, prospective, observational study evaluating the safety in patients with highly active R(R)MS newly initiating oral cladribine (cladribine cohort) as compared to highly active R(R)MS patients newly initiating fingolimod (comparator cohort). Fingolimod has been selected as the comparator for this study given that both cladribine and fingolimod have oral administration and target a very similar indication, thereby minimizing possible confounding bias by indication and selection bias.

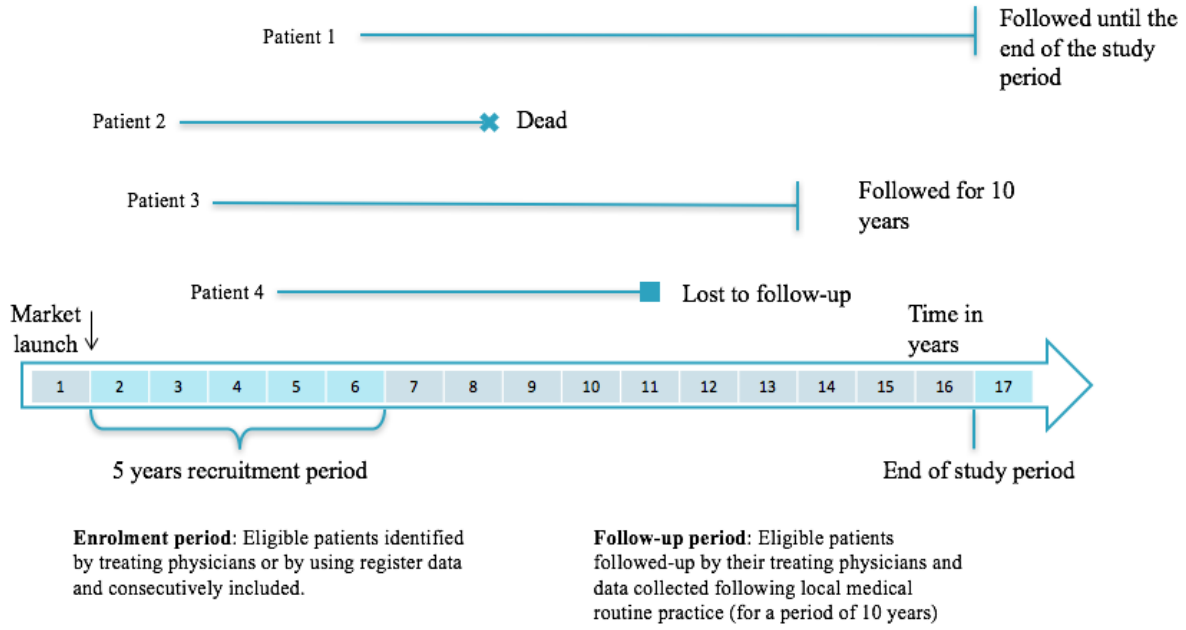
The study is projected to last for a maximum of 15 years, with a maximum 5-year recruitment period and a follow-up of 10 years for each patient. For each patient, data collection will begin after the signature of the informed consent form – noting that patient consent applies to all countries in which additional primary data collection will be conducted and to some countries where secondary use of data will be performed – and continue during 10 years as each patient will be followed for a period of 10 years, except if s/he is lost to follow-up, or withdraws his/her consent, or dies before the end of the follow-up period. Follow-up will continue regardless of oral cladribine or fingolimod discontinuation.

A target sample size of 4,000 patients per cohort is planned to be recruited. Patients newly initiating oral cladribine or fingolimod as part of their routine medical care will be consecutively included in the study by their treating physician (neurologist). The study will only use pre-existing registries or databases and is based on a mixed data collection model relying on both secondary use of data and additional primary data collection where needed to supplement secondary data sources. Indeed, existing data sources (MS registries or national registers) may be supplemented by additional data collection, by adding modules to the existing registries/registers, where needed and where allowed by the registry. This will facilitate collecting variables which are specifically needed for the study, but not routinely collected and readily available in the selected data sources. Please see Section 9.5 for further information on the data sources. Additional data collection will be used in the following MS databases: NeuroTransData database (NTD; Germany) and Multiple sclerosis management system 3D (MSDS 3D; Germany, Spain and Switzerland). The use of secondary data only will be used in the Observatoire Français de la Sclérose en Plaques (OFSEP; France), Italian MS Registry (Italy), Multiple Sclerosis dataBase (MSBase; multi-country) and in the national and MS registries for Denmark, Finland, Sweden and Norway. In Sweden, the completeness of the data in the Swedish MS Registry will be supplemented in combination with Immunomodulation and Multiple Sclerosis Epidemiology Study (IMSE).

The study is planned to start as soon as possible after approval of the protocol by the Pharmacovigilance Risk Assessment Committee (PRAC), approval of the study by required Ethics Committees and approval by any additional regulatory agencies. The availability of oral cladribine on the market in each of the planned countries will determine the country-specific study start as well (depending on market access conditions).

Patient's characteristics at inclusion are defined as the patient's characteristics at the time of treatment initiation. Medical history will be retrieved from the patient's medical record at the time of the inclusion (first clinical assessment) in the databases, using additional primary data collection when needed. In those countries with secondary use of data, medical history of each patient will be retrieved directly in the registers. As the nature of this study is non-interventional, the study does not include any protocol-mandated visits or procedures; data collection will be aligned with local routine medical practices and captured during routine clinical visits. However, in Europe, R(R)MS patients are in general visiting their neurologist every 3 months in half of the countries participating in the study (Denmark, Finland, Germany, the Netherlands, Norway, Switzerland) and every 6 months in the other participating countries (Australia, Belgium, Czech Republic, France, Italy, Spain, Sweden, Turkey, UK). Thus, data will be collected during each neurologist visit, and with a periodicity of at least every 6 months. The data collected are detailed in Section 9.3. Please see Figure 1 for the study timeline.

Figure 1 Study Timeline



9.1.2 Outcomes

9.1.2.1 Primary Outcomes

On cohort level:

- Number of AESIs (severe infections, herpes zoster infection, tuberculosis, PML, other opportunistic infections, and malignancies) in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod.

9.1.2.2 Secondary Outcomes

On cohort level:

- Number of AESI in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod by prior use of immunomodulatory/ immunosuppressive agents ;
- Number and duration of severe lymphopenia events in patients with highly active R(R)MS newly initiating oral cladribine;
- Number of patients by DMT (immunosuppressive or immunomodulatory agents) after oral cladribine treatment in patients who experience a recurrence of the disease activity in patients with highly active R(R)MS newly initiating oral cladribine.

9.1.2.3 Exploratory Outcomes

Exploratory outcomes reflect outcome data that might have low completeness or heterogeneity of data collection in participating registries and data sources. On cohort level:

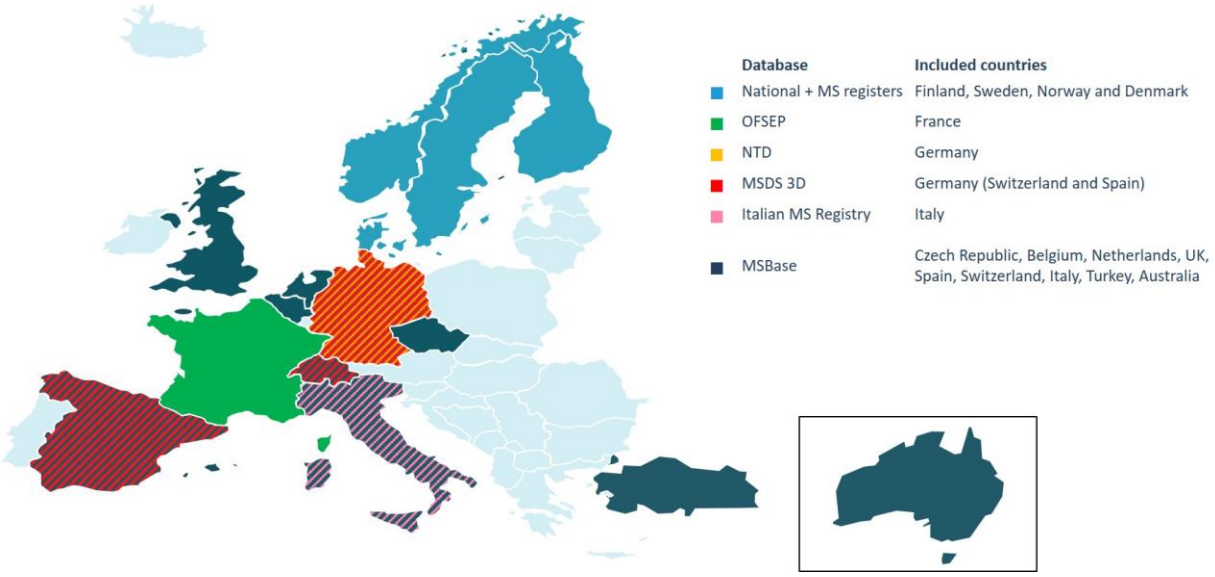
- Number of patients discontinuing treatment, overall and by reasons for discontinuation in patients with highly active R(R)MS newly initiating oral cladribine or fingolimod;
- Number and time points of severe lymphopenia and AESI in patients with highly active R(R)MS newly initiating oral cladribine.

9.2 Setting

The study population is expected to be recruited by health care providers (HCPs) who manage MS patients (e.g. neurologists), or selected in national healthcare registers and MS registers in the Nordic countries and countries participating in Multiple Sclerosis dataBase (MSBase). The following parts of the document are divided into two where necessary, to reflect the two different ways the study population will be selected (either based on secondary use of data only, or in data sources complemented with additional primary data collection).

The following databases will be included: Observatoire Français de la Sclérose en Plaques (OFSEP; France), NeuroTransData database (NTD; Germany), Multiple sclerosis management system 3D (MSDS 3D; Germany, Spain and Switzerland), Italian MS Registry (Italy), Multiple Sclerosis dataBase (MSBase; multi-country) and the Nordic national and MS registers (Denmark, Finland, Norway and Sweden) (see Figure 2 below). The data sources are further described in Section 9.5.

Figure 2 Map of the Countries to be Included in the Study



9.2.1 Data Sources and Data Collection

The data collection in this study is based on pre-existing MS registers and data sources in multiple countries, mostly across Europe, from representative MS patient populations and involves secondary use of data complemented with additional primary data collection. in some countries where supplemental data is needed due to more limited secondary data sources. Additional primary data collection will be set up in data sources only when it is possible to add additional data collection modules to the established data collection system of the registry or database.

Data sources and study countries were selected for inclusion based on feasibility of acquiring data for the purposes of this study, as well as a history of high quality data, availability of the minimum dataset, estimated counts of patients with active records, and the possibility for long-term follow-up given the long-term nature of this study.

9.2.1.1 Secondary Use of Data

In Denmark, Finland, France, Italy, Norway and Sweden, as well as in countries involved through MSBase, data will be retrieved from routinely captured data in existing data sources. For the national healthcare registers, the whole population of each country is covered (Nordic countries), whereas the MS registers by definition cover part of the population (see Section 9.5).

According to the legislation in Denmark, Finland, Norway and Sweden, no patient consent is needed when the data from the national healthcare registers are used for scientific research. In addition, the data in the Swedish MS registry and in the Norwegian MS Registry and Biobank are collected based on an existing patient consent that covers also use of the data for scientific research. In some cases, additional patient informed consent forms or information letters indicating that the data will be transferred to another organization for analysis may be required and will have to be obtained from individual patients (e.g., MSBase and OFSEP). Withdrawal from the national

healthcare registers is not possible and loss to follow-up can only occur because of emigration or death.

9.2.1.2 Additional Primary Data Collection

Additional primary data collection will be set up in selected sites from the network of neurological centers contributing to the MSDS 3D and NeuroTransData (NTD) database. The sites are primarily located in Germany with additional sites in Switzerland and Spain.

Eligible patients will be included in the study by the treating physicians who manage MS patients in participating sites from the pre-existing registries at the time of presentation for a routine clinic visit. The pre-existing registries in this situation act as a network of neurological centers. All R(R)MS patients newly initiating oral cladribine or fingolimod during the enrolment period will be assessed for eligibility and all eligible patients will be consecutively proposed to enter the study. After signing the informed consent, the additional primary data is collected directly from the patient by the treating physician using an electronic data capture system specifically designed for the purpose of this study or using an existing data collection system augmented with study-specific modules to capture information not readily available in the existing data collection system (additional data collection).

The specifications of the electronic data capture system/additional modules will be developed according to the study protocol and will be used to capture all the variables required specifically for the study.

9.2.2 Study Population

The study aims to include at least 4,000 patients per cohort from centers specialized in the management and treatment of MS patients over a maximum 5-year recruitment period. For detailed information on sample size calculations, see Section 9.6.

The study population will be identified according to the below inclusion and exclusion criteria.

For inclusion of a patient in the study, all of the following inclusion criteria must be fulfilled:

- Newly initiating oral cladribine or fingolimod according to local label for MS;
- Written informed consent is obtained (in all countries for which the mixed model applies (secondary data supplemented with primary data) and in some countries where only secondary data is used).

Patients are not eligible for this study if they fulfill any of the following exclusion criteria:

- Received fingolimod prior to initiating oral cladribine;
- Received oral cladribine prior to initiating fingolimod.

9.2.3 Definition of Study Cohorts and Description of Treatments

The oral cladribine cohort includes patients with highly active R(R)MS, newly initiating oral cladribine in accordance with the locally approved label, and naïve to fingolimod. The comparator cohort is composed of patients with highly active R(R)MS newly initiating fingolimod, also in accordance with the locally approved label, and naïve to oral cladribine. Patients are considered as newly initiating their treatment if they never had a prescription of the treatment of interest before.

To define exposure, the following variables will be considered in both cohorts: date of treatment initiation, dosing and schedule, date of discontinuation and reasons for discontinuation, and cumulative exposure (mg/kg of body weight).

The recommended cumulative dose of oral cladribine is 3.5 mg/kg body weight over 2 years, administered as one treatment course of 1.75 mg/kg per year, followed by observation for another 2 years. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (1 or 2 tablets) as a single daily dose, depending on body weight.

The recommended dose of fingolimod is one 0.5 mg capsule taken orally once daily.

As this is a non-interventional study, the decision to prescribe one or the other DMT (oral cladribine or fingolimod) occurs before the decision to include the patients into the study and is thereby not influenced by participation in the study.

9.2.4 Study Period

Cohort entry date is defined as the date a patient newly initiates cladribine or fingolimod. The cohort entry date can only be after cladribine has become available in the country participating to the study.

In the data sources using additional primary data collection, patients will be followed from the cohort entry date after they have signed the informed consent until the end of the data collection period (10 years), loss to follow-up, withdrawal of their informed consent or death, whichever comes first. In the data sources with secondary use of data only, patients will be followed from the cohort entry date until the end of the data collection period (10 years), emigration, or death, whichever comes first. The overall study duration is estimated to be of maximum 15 years in both cohorts, based on an estimated recruitment period of 5 years and a follow-up of 10 years for each patient.

Due to the prolonged action of oral cladribine and the potentially long latency period of some of the study outcomes, patients who discontinue the study treatment will still be followed until the end of the 10-year period after enrolment, even if the patients switches to any other DMT.

9.2.5 Frequency of Assessments

No additional visits to the HCP outside of routine practice will be mandated by the protocol. Data collection is conducted according to local routine medical practices and data are captured during routine clinic visits. However, it is expected that data will be collected with a periodicity of at least 6 months over the full study period, based on current practices regarding management of patients with R(R)MS in Europe and other participating countries. Study outcomes (malignancies, severe and/or serious infections, opportunistic infections, lymphocyte counts [if performed according to routine practice], treatment discontinuation and reasons for discontinuation) will be mandatory variables and will be collected during each routine clinical visit. In the data sources with secondary use of data, the data collection will be event-based: the data collected will include only the variables the physician has considered as relevant to be recorded during the visit. All entries recorded in these data sources will be captured. In this real-world setting, the frequency of visits is also expected to be dictated by disease complications or occurrence of AEs.

9.2.6 Withdrawal from the Study

In the data sources based on patient consent, patients may withdraw their consent to participate in the study at any time, with no effect on their medical care or access to treatment. All information already collected as part of the study until the date of withdrawal will be retained for analysis; however, no further information regarding the patient will be collected. Other reasons of withdrawal are death or lost to follow-up. In countries, where the data are collected without consent (based on national legislations), patients cannot withdraw from the study, but other reasons for withdrawal are emigration or death.

9.3 Variables

9.3.1 Variables Collected at Enrolment and in Follow-up

The data sources to be used allow the collection of data at enrolment and during the follow-up of the patients. All data will be collected as per local routine practice, i.e., treatment and procedures are prescribed based upon the treating physician's decision. Variable definitions will be presented in Appendix 1.

At enrolment (ie, at time of treatment initiation):

- Demographics: sex, age at enrolment

Disease history:

- Date of diagnosis of MS
  - Date of onset of MS, if available
  - Disease clinical course at enrolment
  - Expanded Disability Status Scale (EDSS) within 1 year prior to enrolment (using the measurement closest to enrolment)
  - Number of relapses within 1 year prior to enrolment

- DMT history: generic or trade name, dose, as well as the starting and stopping dates.

- Medical history:
  - History of diseases of interest including history of malignancies, virus hepatitis C status, virus hepatitis B status, human papillomavirus (HPV) status, herpes zoster, varicella and other infections
  - History of Grade ≥1 lymphopenia (based on the closest assessment made before study enrolment), severe and/or serious infections, opportunistic infections, arrhythmias, bradyarrhythmias, QT interval prolongation, macular edema, hypertension, severe respiratory disease, pulmonary fibrosis, chronic obstructive pulmonary disease, renal impairment, hepatic impairment, and liver disease
- Concomitant medications: all prescriptions taken by the patient within 28 days before enrolment will be recorded including corticosteroids taken for the management of relapses, and prior immunosuppressive (IS)/immunomodulatory (IM) agents (other than DMTs).
- Vaccines: name (eg, herpes zoster vaccine) and date.

<u>During follow-up:</u>

- Date and reasons for discontinuation of oral cladribine and fingolimod treatments, when relevant.
- DMT: generic or trade name, dose, as well as the starting and discontinuation dates, with reasons for start/ discontinuation.
- Concomitant medications, including immunosuppressive / immunomodulatory agents (other than DMTs) such as corticosteroid treatment.
- Date of death, if applicable.

9.3.2 Outcome Variables

The study-specific data will be registered for each of the following events:

- Malignancies, grouped and by individual type (see Section 9.4.2);
- Severe infections, that includes four categories: tuberculosis, PML, other opportunistic infections, and other severe infections;
- Severe lymphopenia;
- Herpes zoster infection, regardless of severity, and including severe herpetic infection.
- Treatment discontinuation
- Reason for treatment discontinuation

For complete and accurate information, the data collected on these pre-defined events will include as much detail as possible to corroborate diagnosis, including but not limited to histopathologic results, and relevant laboratory and imaging results.

If oral cladribine or fingolimod treatment is discontinued, the reasons for discontinuation and the data related to administration of any other DMT post-cladribine or post-fingolimod will be recorded.

9.3.3 Predefined Risk Factor Variables

Risk factors for the outcomes of interests are:

At enrolment:

- Any personal and family history of malignancy
- Female hormones (eg, oral contraceptives, hormonal replacement therapy)
- History of prior IS/IM therapy with the following categories: no IS/IM, at least one IS, two different IS received, ≥ 3 different IS received, at least one IM, two different IM received, ≥ 3 different IM received, at least one IS and one IM. The duration of the last IS or IM used will be recorded in months.
    - IM agents: Interferon beta-1a, -1b, glatiramer acetate, pegylated interferon beta 1-a
    - IS agents: Azathioprine cyclophosphamide, mitoxantrone, mycophenolate mofetil, azathioprine, leflunomide, natalizumab, alemtuzumab, dimethyl fumarate, methotrexate, rituximab, tacrolimus, fingolimod, teriflunomide, daclizumab, antineoplasic agents, corticosteroids for systemic use, other immunosuppressive agents
- Infection status (eg, HPV status)
- Use of female hormones
- Concomitant medications, including immunosuppressive/ immunomodulatory agents (other than DMTs) such as corticosteroid treatment
- Radiation exposure (eg, tanning beds)
- Alcohol consumption
- Smoking
- Obesity

During follow-up with their respective dates are of interest for the study outcomes:

- Female hormones (eg, oral contraceptives, hormonal replacement therapy)
- IS / IM therapy with the following categories (as defined above)
- Infection status (eg, HPV status)
- Radiation exposure (eg, PET scans and tanning beds)
- Alcohol consumption
- Smoking
- Obesity

Derived and transformed data needed for the analysis are described in Section 9.8.2.

9.4 Variable Definitions

9.4.1 Exposure Definition

Exposure to oral cladribine or fingolimod will be documented based on the date of the first prescription or record of treatment in the selected data sources. In the Nordic countries, the MS drug exposure data will be primarily collected from the MS registers and can be complemented with the data from the Prescription registers. As the objective of this observational study is to evaluate long-term safety in patients newly treated with oral cladribine or fingolimod in routine clinical practice, there will be no restriction on possible concomitant treatments in the enrolled patients. Concomitant treatments will be recorded as described above in Section 9.3. In the Nordic countries, data on concomitant medications will be collected both from MS registers and Prescription registers.

For both cohorts, data regarding unit dose, frequency of administration, duration of therapy (start and stop dates), and dose adjustments will be collected, if feasible. Continuation and subsequent changes in oral cladribine and fingolimod treatments will be based on the data as captured in the data sources.

Primary exposure definition (Intention-to-treat)

The intention-to-treat exposure will be classified in the following mutually exclusive categories:

- Oral cladribine at enrolment;
- Fingolimod at enrolment;

and is defined as the first study drug prescribed at enrolment, with at least one day of treatment, regardless of subsequent treatment discontinuation or switch.

As-treated exposure definition

The as-treated exposure definition is defined as time-dependent exposure indicating on-going treatment with the following mutually exclusive categories:

- Current exposure to oral cladribine;
- Current exposure to fingolimod

At treatment switch from oral cladribine to fingolimod and vice versa, current exposure will be extended by a washout period of 6 months for the discontinued treatment after which the exposure to the newly initiated treatment will start.

Time since last dose received

Treatment with oral cladribine and fingolimod will be classified in the following mutually exclusive categories of exposure:

- Current use: for ongoing treatment;
- Recent use: Days 1-365 after date of last dose received;
- Past use: more than 1 year after date of last dose received.

9.4.2 Outcome Definitions

Malignancy: Any occurrence of malignant neoplasms during the study period. These will be grouped and classified by type. Malignancies will include all pathologically confirmed solid tumors (excluding non-melanoma skin cancer) and hematological malignancies, as the primary outcome for all malignancies-related analyses. Benign tumors will not be collected. The pre-defined groups are the following:

- Any malignancies excluding non-melanoma skin cancer (NMSC) (primary)
- Any malignancies including NMSC
- Solid tumors only
- Hematological tumors only

Severe infections:

The following categories will be investigated:

- Tuberculosis
- PML
- Opportunistic infections (excluding herpetic infections, tuberculosis, and PML): defined as an invasive infection caused by microorganisms that are normally non-pathogenic or rarely pathogenic in individuals with normal immune function or cause an infection of a type or severity not seen in the normal host.
- Other severe infections

All bacterial, viral, fungal, parasitic and protozoal infections that occur during the study period and regardless of the duration of infection will be recorded. The duration of infections will be the difference between start date and recovery date as reported by the treating physician. Patients may contribute for more than one episode to this analysis if, after resolution as defined, another infection occurs.

An infection will be considered severe if it leads to a significant impairment of functioning, i.e., the subject is unable to carry out usual activities. This definition includes serious and non-serious infections, in line with the definition used in the RMP of oral cladribine. An infection is considered serious if it fulfills at least one of the following seriousness criteria: results in death, is life-threatening, requires in-patient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or is otherwise considered as medically important.

As the availability of data related to certain infections may vary among the databases, detailed operational definitions for the identification of severe and opportunistic infections in different disease coding systems used by data sources of the study will be defined in the statistical analysis plan (SAP).

Herpes zoster infections: Regardless of the severity.

Severe lymphopenia: Any occurrence of severe lymphopenia during the study period, classified as Grade ≥3. As per the Common Terminology Criteria for Adverse Events (CTCAE) (V4.03: June 14, 2010) from the National Institutes of Health, the grades of lymphopenia are defined based on laboratory test results that indicate a decrease in number of lymphocytes in a blood sample:

- Grade 3: <500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L
- Grade 4: <200/mm^3; <0.2 x 10^9 /L

Duration of severe lymphopenia: Defined as the interval from the finding of severe lymphopenia until resolution, which is achieving a CTCAE Grade 1 (less than lower limit of normal [LLN] to 0.8 x 10^9 /L) or normalization (above LLN). Patients may contribute for more than one episode to this analysis if, after resolution as defined, severe lymphopenia occurs. The frequency of lymphocyte counts in patients with severe lymphopenia will be described with special emphasis on the number and timing of lymphocyte counts in relation to oral cladribine dosing.

Treatment interruption: In the oral cladribine cohort, discontinuation will be further defined as stopping the treatment before completion of a treatment course. Discontinuation will be considered temporary if the patient restarts the same or the second treatment course with a delay of up to 6 months. Otherwise, it will be considered permanent. With regards to discontinuation in the fingolimod cohort, it will be considered as temporary discontinuation if the patient restarts fingolimod within 90 days after temporary discontinuation or permanent discontinuation if there are no more records of fingolimod thereafter.

Treatment discontinuation: Treatment discontinuation will be directly recorded by the treating physician and includes any permanent treatment discontinuation (excluding treatment interruption), regardless of the reason for discontinuation. Reasons and dates for discontinuation will also be captured. The treatment stop date will be used to derive the date of treatment discontinuation.

For complete and accurate information, for each of the outcomes defined above, the data collected will include as much detail as possible to corroborate diagnosis, including but not limited, to histopathologic results, and relevant laboratory and imaging results. In addition, the following two outcome categories will be differentiated:

- Reported outcomes: defined as all outcomes reported by physicians with no additional elements to corroborate the diagnosis;
- Confirmed outcomes: defined as all outcomes reported by physicians with any additional elements to corroborate the diagnosis such as histopathology for malignancies.

DMT after cladribine treatment: Sequential use of any DMT (immunosuppressive or immunomodulatory agents) after cladribine treatment in patients who experience a recurrence of the disease activity.

9.5 Data Sources

The databases included in this study were selected based on a feasibility assessment made according to the study design as described in more detail in Section 9.2.1. In short, the selected data sources have been established for many years and are considered to have complete, high quality coverage of their respective regions (Ziemssen 2016). The study database will be based on data coming from several data sources as described in Section 9.2.1. Table 1 describes data sources based only on secondary data collection and Table 2 describes the data sources with additional primary data collection.

9.5.1 Secondary Use of Data only

Table 1 describes the databases with no additional primary data collection (only secondary use of data) and their population coverage.

Table 1 Data Sources with Secondary Data Collection (Secondary use of Data)

Data source, per country	Population coverage in 2016
DENMARK	
MS registers	
Danish Multiple Sclerosis Registry	100% of Danish MS patients (personal communication with the register holder (February 2017))
Danish MS Treatment Register	100% of Danish MS patients with DMT
National healthcare registers	
Registry of Medicinal Product Statistics	100% of the population with prescribed drugs purchased in community pharmacies in Denmark
Danish National Patient Register	100% of the population with somatic inpatient or special outpatient care in Denmark
Danish Cancer Register	100% of the population with cancer in Denmark
Danish Register of Causes of Death	100% of the deceased population in Denmark
FINLAND	
MS registers	
Finnish MS data collection system	13/20 hospital regions in Finland (personal communication with the register holder (March 2017))
National healthcare registers	
Prescription registers	100% of the population with prescribed reimbursed drugs purchased in community pharmacies in Finland e-register: 100% of the population with prescribed drugs purchased in community pharmacies in Finland
Care Register for Health Care (HILMO; secondary care)	100% of the population with inpatient or special outpatient care visits in Finland

Data source, per country	Population coverage in 2016
Register of Primary Health Care Visits (AvoHILMO)	100% of the population with publicly organized primary care in Finland
Finnish Cancer Registry	100% of the population with cancer in Finland
National Infectious Diseases Register	100% of the population diagnosed with one of the 70 selected infectious diseases in Finland
Cause of Death Register	100% of the deceased population in Finland
FRANCE	
OFSEP	Approximately 50% of French MS patients
ITALY	
Italian MS registry	57 sites across Italy, approximately 80% (20,000 patients) of the Italian MS patients (Flachenecker et al., 2014)
NORWAY	
MS registers	
Norwegian MS Registry and Biobank	Approximately 55% (6,000 patients) of the Norwegian MS patients (Myhr et al., 2015)
National healthcare registers	
Norwegian Prescription Database	100% of the population with prescribed drugs dispensed in pharmacies in Norway
Norwegian Patient Registry	100% of the population with inpatient or special outpatient care visits in Norway
Cancer Registry of Norway	100% of the population with cancer in Norway
Cause of Death Registry	100% of the deceased population in Norway
SWEDEN	
MS registers	
Swedish MS Registry	Approximately 80% (14,500 patients) of the Swedish MS patients (Hillert et al., 2015)
National healthcare registers	
Swedish Prescribed Drug Register	100% of the population with prescribed drugs purchased in community pharmacies in Sweden
National Patient Register	100% of the population with inpatient or special outpatient care visits in Sweden
Swedish Cancer Register	100% of the population with cancer in Sweden
Cause of Death Register	100% of the deceased population in Sweden
MULTI-COUNTRY	
MSBase[a,b]	Approximately: 48 sites, 24 972 MS patients • Australia: 20 sites, 4,314 patients • Belgium: 4 sites, 877 MS patients • Czech Republic: 2 sites, 3,499 MS patients • The Netherlands: 3 sites, 839 MS patients • Spain: 8 sites, 2,471 MS patients • Switzerland: 2 sites, 491 MS patients • Italy: 10 sites, 4,606 MS patients • Turkey: 6 sites, 2,764 MS patients • UK: 3 sites, 505 MS patients

OFSEP = Observatoire Français de la Sclérose en Plaques
MSBase = Multiple Sclerosis database.
[a] Number of MS patients with at least 1 visit between January 1, 2014 and December 31, 2016.

[b] Proportion of total MS population is not available.

Each of the data sources listed in Table 1 is further described in Appendix 2.

In the Nordic countries, every resident has a Personal Identity Number (PID). All the registers listed in Table 1 include the PID, enabling linkage of the data across all registers and thus capture of the needed data for the study. The data linkage is described in further detail in Section 9.7.1.

9.5.2 With Additional Primary Data Collection

Table 2 describes the data sources using specific primary data collection in addition to data which are already collected in routine, in existing MS registries or databases, and their population coverages. In Germany, data sources include both MSDS 3D and NTD. The data will be collected using a unified data collection system based on the MSDS 3D database, taking into account removal of potentially overlapping clinics and patients.

Table 2 Data Sources Using Additional Primary Data Collection (Mixed model)

Data source, per country	Population coverage in 2016
GERMANY	
NTD	73 sites across Germany, approximately 25,000 MS patients
MSDS 3D (incl. also Switzerland and Spain)	The database is used purely for specific studies and all patients will be recruited per study protocol

MSDS 3D = Multiple Sclerosis Management System 3D
NTD = NeuroTransData

9.6 Study Size

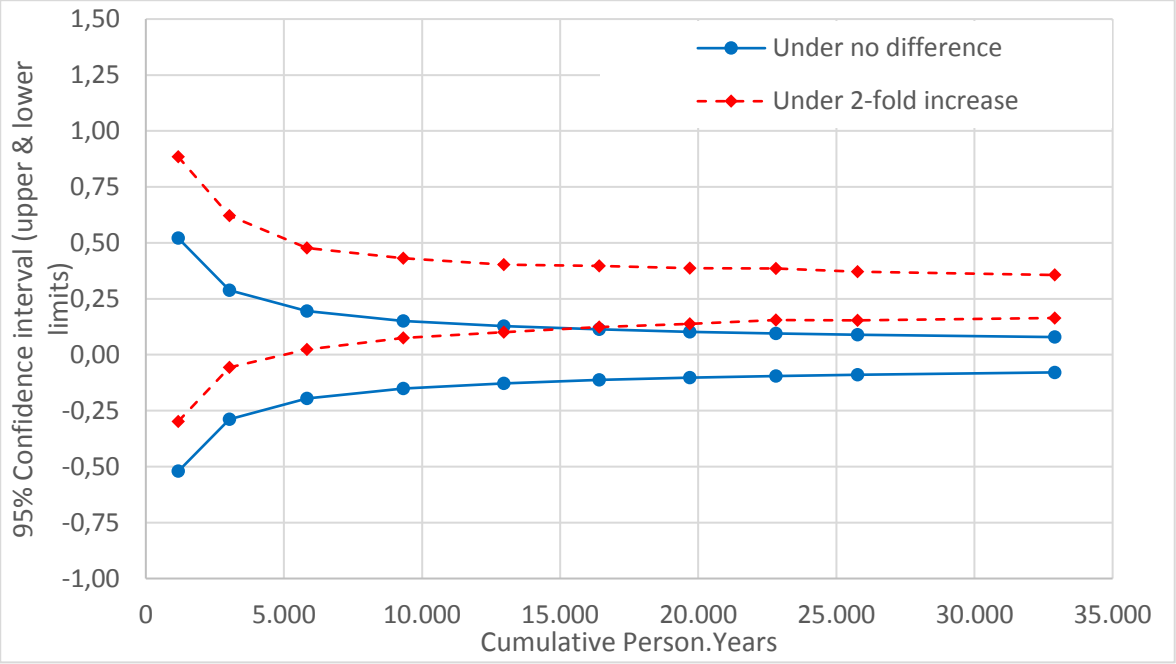
Oral cladribine is expected to target a similar population as fingolimod (highly active R(R)MS). Applying this information with the anticipated study design and using databases from the participating countries listed in Section 9.2.1, the recruitment of the planned 4,000 patients per cohort within a period of 5 years seems a reasonable and feasible target, allowing a 10-year follow-up per patient over a 15-year study period in total.

However, at this stage there are still some unknowns and reaching the target sample size will likely be influenced by several factors. Patient recruitment is subject to acceptance of oral cladribine by prescribing neurologists and patients within the MS treatment landscape. The setting (i.e., hospital and/or private practice) in which oral cladribine patients will be treated and managed also has an influence on participants' recruitment in the databases using additional primary data collection as does the organizational structure of these databases. Considering the primary objective, the study size estimation is based on simulated data and is driven by malignancy (AESI having the lowest incidence rate among the list of different AESI for this study). Figure 3 (A & B) and Figure 4 (A & B) present the level of accuracy of the risk difference and relative risk estimates, assuming no or a 2-fold risk of malignancy among cladribine patients in comparison to the background population, and a sample size of 4,000 patients per cohort recruited over 5 years.

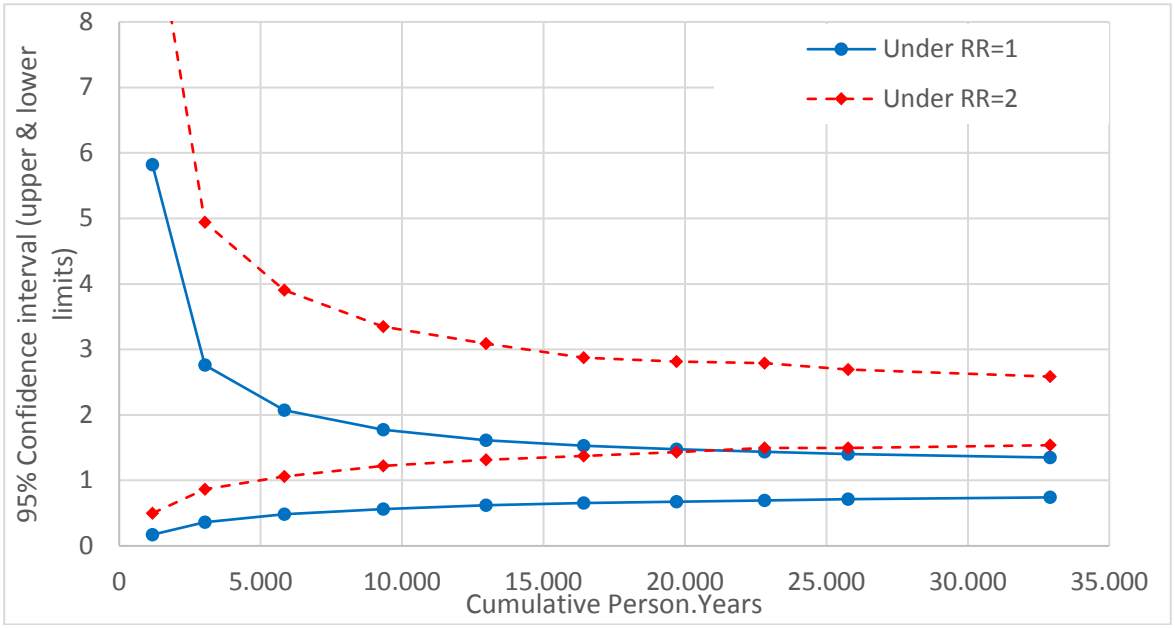
The recruitment assumption in the simulation is based on information provided by the OFSEP during the feasibility assessment in terms of patients enrolled into their network after launch of fingolimod, with a somewhat conservative approach based on a lower number of patients enrolled in the initial years that increases progressively over time and a drop-out rate of about 5% every subsequent year. The actual recruitment will be influenced by any information on product safety and efficacy, or other information that the physician might have. In the simulation, 2 scenarios in terms of incidence rate have been considered: 0.26 and 0.40 cancers per 100 person-years. In the cladribine clinical trial program, the incidence rate of malignancies per 100 person-years in patients exposed to cladribine (n=1,976) was 0.37, which is close to 0.40.

Figure 3 Background Incidence of 0.26 Cancers per 100 Person-years (GLOBOCAN, 2012) (A and B)

A. Risk Differences (per 100PY)



B. Relative Risks

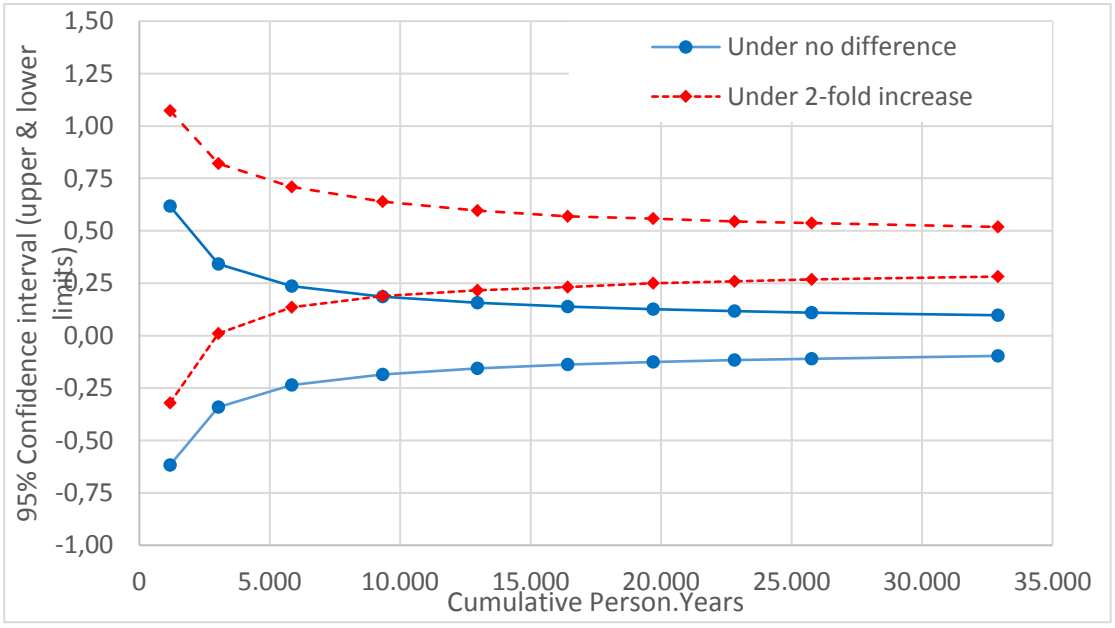


Source: Ferlay, 2013, GLOBOCAN 2012.

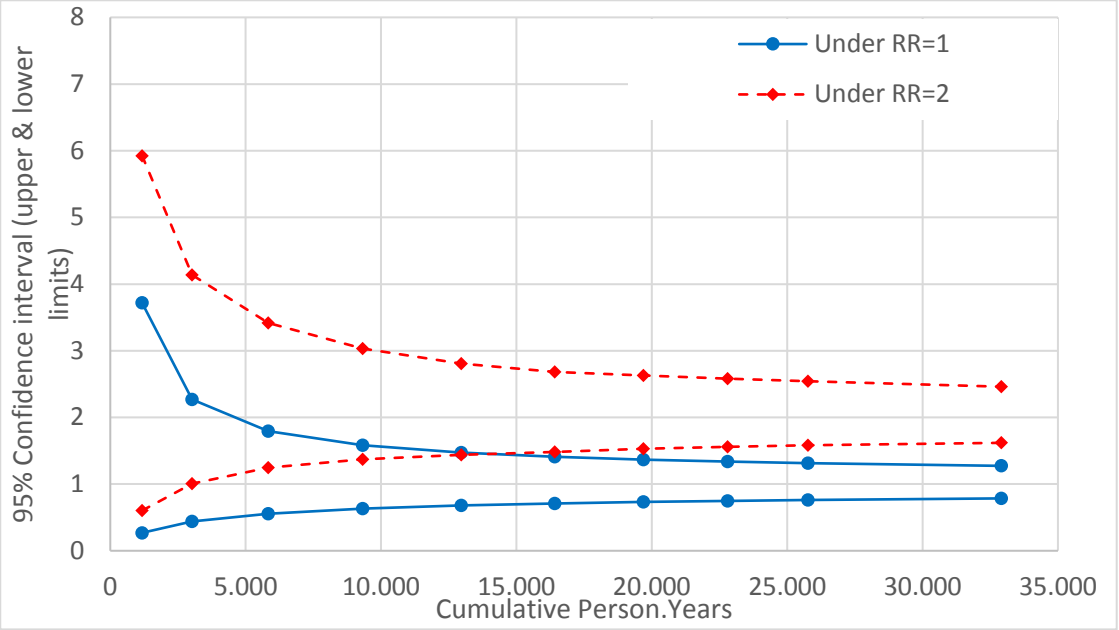
PY: person-years; RR: Relative Risk. Method: Confidence intervals (CIs) using Miettinen and Nurminen method (1985) for risk differences and mid-P approach (software R 3.1.2, Epitools package) for relative risks with no adjustment for interim analysis. Duration of the study will depend on the actual recruitment rate.

Figure 4 **Background incidence of 0.40 cancers per 100 person-years (GLOBOCAN, 2012) (A and B)**

A. Risk Differences (per 100 PY)



B. Relative Risks



Source: Ferlay, 2013, GLOBOGAN 2012.

PY: person-years; RR: Relative Risk.

Method: Confidence intervals (CIs) using Miettinen and Nurminen method (1985) for risk differences and mid-P approach (software R 3.1.2, Epitools package) for relative risks with no adjustment for interim analysis. Duration of the study will depend on the actual recruitment rate.

Table 3 presents the probability of excluding an increased incidence risk below 2, 1.5 or 1.3 times the expected background incidence rate (i.e., upper limit of 95% incidence rate difference below 1, 0.5 or 0.3 times the background incidence), as well as the probability of reaching statistical significance (i.e., lower limit of 95% incidence rate difference above 0) for different background incidences, study durations and expected incidence rates in the cladribine cohort. The results in Table 3 are gained by simulation.

Table 3 Distribution of the Probabilities to Exclude Rate Differences for Different Background Incidences, Study Durations and Expected Incidence Rates in Cladribine Patients

Background Incidence	Study Timing	Patients Follow-up	Expected Incidence in cladribine patients /100PY	Probability to exclude a rate difference			
/100 PY	Years	Person Years		below 1*BI	below 0.5*BI	below 0.3*BI	above 0
0.260	5	9,327	0.338	59%	9%	2.5%	17%
0.400	5	9,327	0.520	78%	12%	2.66%	23%
0.260	5	9,327	0.260	91%	40%	17.3%	2.6%
0.400	5	9,327	0.400	99%	58%	25.6%	2.3%
0.260	10	25,767	0.338	95%	18%	2.9%	39%
0.400	10	25,767	0.520	99%	28%	2.7%	52%

Background Incidence	Study Timing	Patients Follow-up	Expected Incidence in cladribine patients /100PY	Probability to exclude a rate difference			
/100 PY	Years	Person Years		below 1*BI	below 0.5*BI	below 0.3*BI	above 0
0.260	10	25,767	0.260	100%	81%	41.3%	2.7%
0.400	10	25,767	0.400	100%	94%	58.0%	2.6%
0.260	15	32,907	0.338	99%	23%	2.3%	45%
0.400	15	32,907	0.520	99.9%	32%	2.8%	63%
0.260	15	32,907	0.260	100%	89%	49.6%	3.0%
0.400	15	32,907	0.400	100%	98%	68.2%	2.6%
0.260	15	32,907	0.338	99%	23%	2.3%	45%
0.400	15	32,907	0.520	99.9%	32%	2.8%	63%
0.260	15	32,907	0.260	100%	89%	49.6%	3.0%
0.400	15	32,907	0.400	100%	98%	68.2%	2.6%

Source: Ferlay, 2013.

BI: Background Incidence; PY: person-years

Method: Based on 10,000 simulations using binomial distribution. Confidence intervals (CIs) using Miettinen and Nurminen method (1985) on with no adjustment for interim analysis. Study Duration will depend on the actual recruitment rate.

It is important to note that “Study Timing” in the second column of Table 3 and Table 4 reflect the years from the first participant enrolled. For instance, year 5, shows the accrued patient-years up to 5 years since the first participant enrolled, and not patients-years when all participants have completed 5 years of follow-up.

At Year 5, for a background incidence of 0.4 per 100 person-years (PY) and no difference in incidence rates between cohorts, there is 99% power to rule out a malignancy rate difference of 1 times the background incidence rate (ie, 99% probability that upper limit of 95% CI of rate difference is below 0.4 per 100 PY).

At Year 10, for a background incidence of 0.26 per 100 PY and no difference in incidence rates between cohorts, there is 81% power to rule out a malignancy rate difference of 0.5 times the background incidence rate (ie, 81% probability that upper limit of 95% CI of rate difference is below 0.13 per 100 PY).

At Year 15, for a background incidence of 0.26 per 100 PY and no difference in incidence rates between cohorts, there is 89% power to rule out a malignancy rate difference of 0.5 times the background incidence rate (ie, 89% probability that upper limit of 95% CI of rate difference is below 0.13 per 100 PY).

Similarly, Table 4 below provides the probability to exclude a relative risk below 2 or a 1.5-fold increase, as well as to reach statistical significance (relative risk above the unit) for different background incidences, study durations and expected relative risks.

Table 4 Distribution of the Probabilities to Exclude a Relative Risk Below 2, 1.5 or Above 1 for Different Background Incidences, Study Durations and Expected Relative Risks

Background Incidence	Study Timing	Patients Follow-up	Assuming True RR	Probability to exclude a RR		
/100 PY	Years	Person Years		below 2	below 1.5	above 1
0.260	5	9,327	1.3	35%	8%	16%
0.400	5	9,327	1.3	49%	10%	22%
0.260	5	9,327	1	67%	30%	2.5%
0.400	5	9,327	1	84%	42%	2.3%
0.260	10	25,767	1.3	73%	14%	37%
0.400	10	25,767	1.3	89%	19%	52%
0.260	10	25,767	1	97%	64%	2.6%
0.400	10	25,767	1	100%	82%	2.6%
0.260	15	32,907	1.3	83%	17%	46%
0.400	15	32,907	1.3	95%	24%	62%
0.260	15	32,907	1	99%	74%	2.8%
0.400	15	32,907	1	100%	90%	2.6%
0.260	15	32,907	1.3	83%	17%	46%
0.400	15	32,907	1.3	95%	24%	62%
0.260	15	32,907	1	99%	74%	2.8%
0.400	15	32,907	1	100%	90%	2.6%

Source: Ferlay et al., 2013

BI: Background Incidence; PY: person-years; RR: Relative Risk

Method: Confidence intervals (CIs) based on mid-P approach (software R 3.1.2, Epitools package) with no adjustment for interim analysis. Study Duration will depend on the actual recruitment rate.

9.6.1 Monitoring of patient enrolment

The monitoring of patient enrolment will be summarized, at least twice a year, during the enrolment period by extracting patient counts from the different data sources participating in the study. This will include the evaluation of the number of eligible patients by study cohort (oral cladribine and fingolimod) according to the inclusion and exclusion criteria of the study in each country and data source, as well as the number of drop-outs.

In case of slow enrolment, in one or both study cohorts, actions to increase the study size will be taken during the enrolment period either by including additional sites, adding additional countries or adding new data MS registries. The decision will be made based on the extent of the slow accrual and feasibility assessment for adding additional countries, data sources or sites.

9.7 Data Management

9.7.1 Secondary Use of Data

Study permit approvals and access to the study data will be applied for by the CRO (which will perform the PASS on behalf of the Sponsor) for the part of the study, which is based on secondary use of data. After the identification of the study population from the MS registers, data from each relevant register will be extracted. This will be performed by the register holders. As the data from these registers consist of automatically registered data, independent of the current study purpose, the research question cannot affect the data collection process. Following data extraction, the registry holders will proceed to the data transfer to the CRO according to data permits and patient informed consent. In some cases, additional patient informed consent forms or information letters indicating that the data will be transferred the CRO for analysis may be required and will have to be obtained from individual patients (e.g., MSBase and OFSEP).

A unique dummy Study Identification Number (SID) will be created for each patient, prior to data delivery to the CRO. The CRO will thus receive all raw data without original identifiers. The SIDs will be used for data linkage on an individual level, therefore, the researchers at the CRO level will only have access to data where individuals cannot be directly identified.

9.7.2 Additional Primary Data Collection

When primary data collection is implemented, to supplement secondary data sources, patient data is collected directly by the treating neurologist or designated study personnel using an electronic data capture system specifically designed for the purpose of this study or using an existing data collection system augmented with study-specific modules (additional primary data collection). The specifications of the electronic data capture system / additional modules will be developed according to the study protocol and will be used to capture all the variables specifically required for the study. In addition, the data collection system will include a safety module to allow the reporting of adverse drug reactions according to Section 11.5.

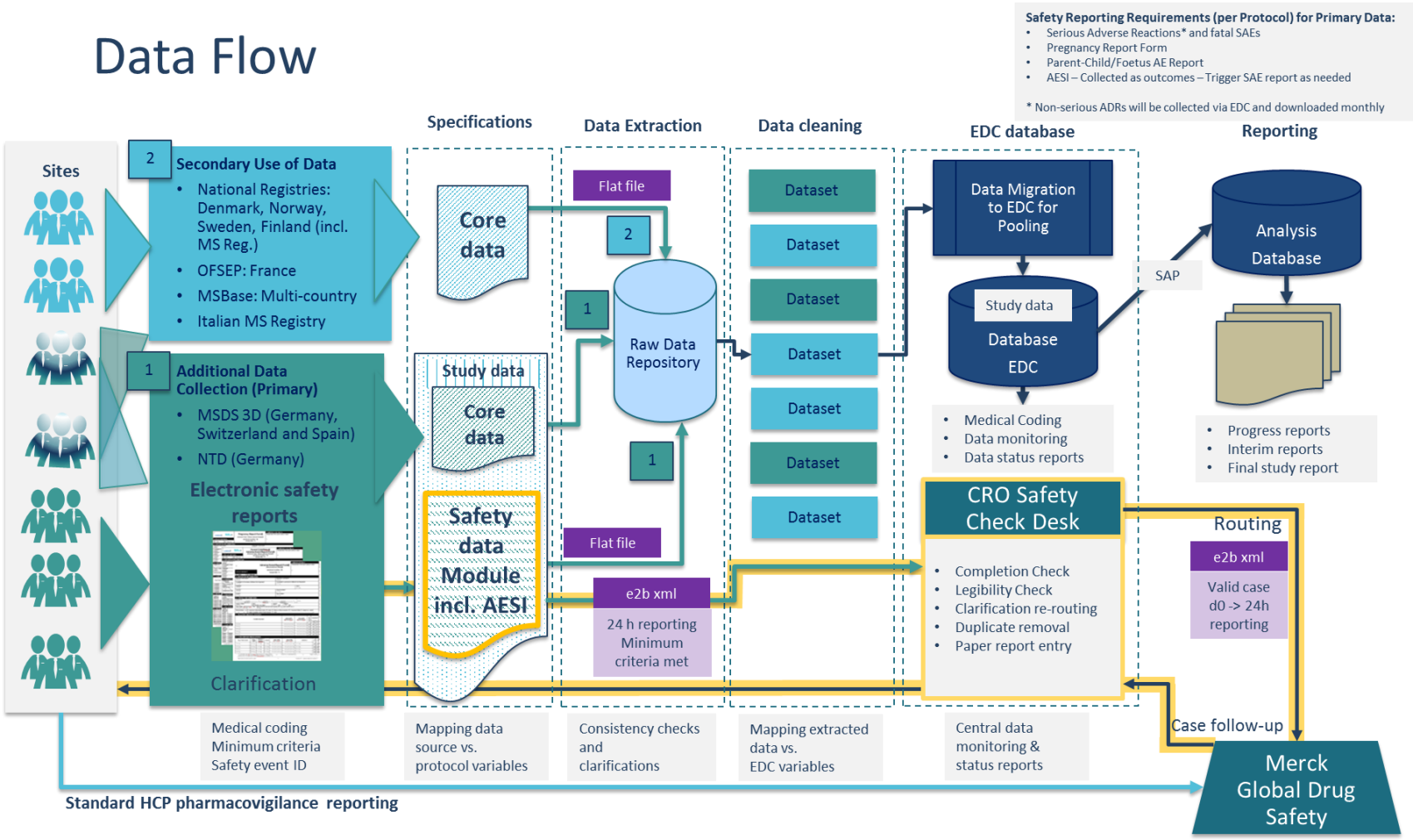
Upon delivery of the data to the Clinical Research Organization (CRO) by the database holders, the CRO will process the data as outlined in Section 9.7.3.

9.7.3 General Data Management

Following data extraction from the data sources (secondary alone or complemented with primary collection), the transferred data will be stored in a raw data repository managed by the CRO under a secure server for data validation and data cleaning procedures. In order to ease the management of data collected from the different data sources participating to the study, an electronic data capture (EDC) system will be used as a central database for all the study data. Data collection modules in the central database will enable the consolidation of the extracted datasets from each of the data sources. This approach will also allow logic checks and data validation checks at the time of data import for swifter identification of any inconsistencies in the data received.

A data migrator tool within the EDC system will be used to map the source data to a consolidated, unified format. It has been identified that some of the data can be collected in the correct format already from the source. Data validation checks can thereby be done during the upload and batch edit checks after the data is merged in the EDC database ensuring further data consistency. The flow chart presented below (Figure 5) describes the process where core data refers to the study variables and outcomes including AESIs collected by the different data sources of the study. The safety reporting track which is applicable only for data sources with additional data collection is highlighted in yellow and described according to the safety reporting requirements in section 11.5. Data extractions for aggregate-level review listings and study progress will be conducted as needed.

Figure 5 Overall data flow from data collection to central EDC database including safety reporting track.



EDC: Electronic Data Capture.

A Data Management plan will be developed to describe all data management processes.in detail and all steps necessary from raw data to final database such as, but not limited to, database development, additional primary data collection process, process for secondary use of data, medical coding considerations and conventions, query edition and database validation.

The Data validation plan will be edited, describing in detail all data checks to be performed on completeness, plausibility and consistency of collected data and identification of data discrepancies and query management based on data cleaning procedures.

R language will be used to create the analysis database, as well as in statistical analysis to create tabulations and graphics, and in all statistical modelling. Full audit trail starting from raw data obtained from register holders and ending to statistical tables and graphs in reports will be maintained. Source code of data management and data analyses is kept for inspection for 5 years after publication of results. The study may be inspected by the Sponsor's independent representative(s), scientific committee, or by the competent authorities.

9.8 Data Analysis

Analyses corresponding to each of the study objectives will be described in full detail in the SAP as a separate document; however, an overview of approaches is provided here.

9.8.1 Analysis Sets

The primary analysis set of patients include patients who follows the intention-to-treat exposure definition as defined in Section 9.4.1.

9.8.2 Derived and Transformed Data

Calculation of person-years of follow-up

Follow-up time for each patient will be calculated from the cohort entry date (initiation of oral cladribine or fingolimod) to the earliest of the following: event of interest, death, end of follow-up, withdrawal of informed consent, emigration or loss to follow-up. For a given non-recurrent event (e.g. first malignancy), the patient follow-up will not be censored for the other events of interest, and the patient will continue to contribute to the risk time for these other events.

Severe lymphopenia duration

Severe lymphopenia duration is defined as the interval from the finding of severe lymphopenia (Grade ≥ 3) until the finding of its resolution (Grade 1 or 0). Given that no regular blood tests are requested per protocol, there is a risk to overestimate the duration of lymphopenia. However, in patients with severe lymphopenia, this risk of bias will be reduced because the physician would be expected to perform a closer follow-up with more frequent blood testing.

Handling of missing data

Methods commonly used in non-interventional studies for handling missing data will be applied. Descriptive analyses will be performed using available data. The number of patients with missing data will be reported for each measured variable in the study. In descriptive analyses, missing data will be described separately and not included in the denominator for the calculation of the percentage for each category of a particular variable.

Full details on handling missing data will be described in more detail in the SAP which will describe the methods for identifying where missing data methods should be applied, the techniques for identifying the type of missing information and the appropriate imputation methods to be used, if any, as per European Medicines Agency (EMA) 2011 guidance on missing data.

9.8.3 Statistical Methods

Descriptive analyses

For continuous variables, the following measures will be reported: the number of patients with non-missing data, the number of patients with missing data, mean, standard deviation, median, quartiles, and minimum and maximum. For categorical variables, the number of non-missing observations (number and percentage of total non-missing; n, % of total), as well as the number of patients with missing data will be reported.

Description of analysis sets and characteristics at enrolment

Number and percentage of patients per cohort (cladribine or fingolimod) will be presented by analysis sets as well as by participant country.

The description of demographic characteristics and other characteristics at enrolment for both cohorts will be presented using summary tables to allow a general comparison. Appropriate statistical tests will be applied to compare the cohorts. Further details on methodology will be provided in the SAP.

Assessment and comparison of safety outcomes

Primary analysis

Using the intention-to-treat exposure definition, the crude and adjusted incidence rates of the different AESIs along with 95% CIs will be estimated in both oral cladribine patients and fingolimod patients. The following categories of AESI will be considered: malignancies (excluding NMSC), herpes zoster infections, tuberculosis, PML, other opportunistic infections, and other severe infections.

To compare the incidence of AESI between oral cladribine patients and fingolimod patients adjusting for key prognostic factors (as defined *a priori* in the SAP for each AESI), the incidence rates ratios of the AESI together with the 95% CIs will be estimated by Poisson regression models

adjusted for the key prognostic factors (including prior use of immunomodulatory/ immunosuppressive agents) and displayed by means of forest plots.

Sensitivity analyses for the primary analysis

The following sensitivity analyses will be performed for the primary analysis:

1) For the analyses regarding malignancies, 2 sensitivity analyses excluding all malignancies occurring within 6 and 12 months after cohort entry will be performed to account for the latency period for malignancies to develop (induction period of 6 and 12 months after treatment initiation).
2) Another set of sensitivity analyses will consider an as-treated analysis. To capture the effect of treatment switch, time-dependent exposure variables indicating on-going treatment (oral cladribine (yes/no), fingolimod (yes/no) will be included in the Poisson regression model. At treatment switch, a latent period of 6 months will be applied to the discontinued treatment. Thus, events occurring within 6 months after the switch will still be considered as related to the discontinued treatment. Censoring at 12 months instead of 6 will also be considered for the analysis regarding malignancies.
3) Another set of sensitivity analyses will consider an on-treatment analysis in which the ITT exposure definition is used but patient follow-up time will be censored 6 months (or 12 months) after oral cladribine or fingolimod treatment discontinuation.
4) Further sensitivity analysis by malignancies grouped will be conducted as follows and described in the SAP: any malignancies including NMSC, solid tumors only, and hematological tumors only.
5) Sensitivity analysis will be conducted using the time since last dose received exposure definition described in Section 9.4.1.
6) As an alternative to the parametric regression analysis, the cumulative incidence of AESIs during follow-up will be described using a non-parametric approach. Details of the description of the analysis will be given in the SAP.
7) , A sensitivity analysis where the analyses are adjusted on propensity scores will be performed. The propensity scores (probability to be included in oral cladribine group at start of follow-up) will be calculated conditional on all potential confounders (eg, key prognostic factors and any other variables possibly associated with treatment selection and/or outcomes).

Secondary analyses

Lymphopenia

The incidence rate of severe lymphopenia in oral cladribine patients as well as the 95% CI will be estimated. The adjusted incidence rates and the 95% CI will be estimated separately for the first severe lymphopenia event and for all the severe lymphopenia events using the Poisson regression adjusting for the key prognostic factors. The results will be displayed by means of forest plots.

While patients have ongoing severe lymphopenia, they are not at risk of a new event of severe lymphopenia, therefore time with ongoing severe lymphopenia will be censored from the analysis.

Analysis of duration of severe lymphopenia will be descriptive using Kaplan-Meier curves stratified by key prognostic factors.

Effect of prior use of immunomodulatory/ immunosuppressive agents on the occurrence of AESI

The effect of the prior use of immunomodulatory (IM) agents or immunosuppressive (IS) agents on the incidence of AESI in patients initiating oral cladribine or fingolimod will be assessed by including such variables into the Poisson regression model. A separate variable will be used for prior IM or IS agents used for treatment of MS and for prior IM or IS agents used for treatment of other conditions than MS.

Description of sequential use of DMT after cladribine treatment in patients who experience a recurrence of the disease activity

Number and percentage of patients that experience a recurrence of the disease activity in both oral cladribine and fingolimod cohorts as well as type of DMT given after oral cladribine or fingolimod (immunosuppressive or immunomodulatory agents), such as switch to fingolimod, oral cladribine, interferons beta-1a, interferons beta-1b, natalizumab, teriflunomide, glatimater acetate, or other DMTs.

Subgroup analyses for the RRMS population

The primary analysis described above will be performed for the subset of patients with RRMS treated with oral cladribine and in all patients included in the fingolimod cohorts. This analysis will be limited to patients with available information on the clinical course of the disease at enrolment.

Exploratory analyses

Description of discontinuation

Number and percentage of patients discontinuing initial treatment (oral cladribine or fingolimod) will be computed for both cohorts, and presented together with the main reasons for discontinuation. Treatment start and discontinuation dates will be taken into account. Kaplan-Meier curves will be used to characterize time to treatment discontinuation.

Relationship between severe lymphopenia and AESI

Relationship between severe lymphopenia and AESI in the oral cladribine cohort will be further evaluated by looking at the temporal associations of the respective events.

The following 2 variables will be constructed:

1) Time since lymphopenia as a continuous variable

2) Number of lymphopenia episodes: 0, 1-2, ≥2.

AESI will be tabulated (number and percentage) with respect to the above variables.

In addition to quantify the temporal association between severe lymphopenia and AESI, the above variables will be added to the analysis of AESI.

Full details on the methodologies mentioned above will be described in the SAP.

9.8.4 Sequence of Analyses

According to the milestones in Section 6, analyses will be performed as part of the additional pharmacovigilance activities for oral cladribine. No control of the Type I error will be implemented and comparison between oral cladribine and fingolimod cohorts will only be performed when enough data has been accumulated in light of the expected background incidence rate. Full details will be described in the SAP.

In addition, further analyses or reporting might be performed to address regulatory requirements and/or to investigate spontaneous reporting safety signals.

9.9 Quality Control

This study will be conducted according to the rules of 'Good Pharmacoepidemiology Practice' (GPP) and the 'Guideline on good pharmacovigilance practices (GVP) – Module VIII (Rev 1)' EMA/813938/2011 Rev 1.

The investigator will comply with the confidentiality policy as described in the site contract, with the requirements described in the protocol. The treating physician is ultimately responsible for the conduct of all aspects of the PASS at the local level and verifies the integrity of all data transmitted to the CRO.

Related quality control mechanisms (eg, data plausibility checks, monitoring of data) will be performed accordingly.

9.10 Limitations of the Research Methods

Selection bias

Selection bias is a distortion of evidence or data that arises from the way that patients are selected and from the completeness of outcome ascertainment (loss to follow-up). Selection bias may arise if the study sample differs substantially from the underlying target population of patients with R(R)MS in the selected countries. Patients with R(R)MS could be referred to multiple medical specialists (neurologists, ophthalmologists, urologists, cardiologists and others) and receive treatment at different types of sites (centers of excellence, university hospitals, general hospitals),

which may in turn be related to disease presentation and degree of severity. To minimize selection bias, the eligibility criteria were selected to be as broad as possible for this study population. In addition, the participating study sites with additional primary data collection will be expected to invite all consecutive eligible patients to participate and sites will enroll patients prospectively during the study period. In the countries with secondary use of data only, all eligible patients will be included during the study period.

Generalizability of results

The generalizability of results and representativeness of the sampled R(R)MS population included in the PASS will be assessed using patients' characteristics at enrolment and known information of the epidemiology of R(R)MS at the time of the report.

Since this study is conducted via secondary use of data through registries, complemented (when needed) or not with additional primary data collection, some countries were not eligible for this study. However, regarding the countries included in this study, those with among the highest MS incidence in Europe, are included, such as the Czech Republic, Finland, Denmark, France, and Norway (11, 9, 7.89, 7.6, and 7 per 100.000 person-years, respectively) (Multiple Sclerosis International Foundation 2013). Italy and Spain (as well as Turkey) are included to represent the southern countries, and those with the second and third highest incidence of tuberculosis of the Western European countries (Spain and UK with 10 and 9.9 cases of tuberculosis per 100,000 population, respectively) (World Health Organization, 2017) are included.

Information bias

Information bias is a distortion in the estimate of association between risk factor and disease that is due to systematic measurement error or misclassification of patients on 1 or more variables, either risk factor or outcome. To preventively minimize this type of bias in the current study, instructions will be provided to all neurologists/ physicians in the centers participating through the databases with additional primary data collection. In the data sources with secondary use of data, the data collection is based on routine clinical practice and cannot be influenced in the context of the study.

As the study is non-interventional, only data from clinical routine practice can be obtained. Therefore, some information may be missing or unavailable. As an example, treatment discontinuation and the association of severe lymphopenia and AESIs might be difficult to assess due to low completion and/or heterogeneity of data collection for these outcomes in the participating data sources. In addition, this may be an issue when measuring the duration of lymphopenia. Given that no regular blood tests are requested per protocol, there is a risk to overestimate the duration of lymphopenia. In patients with severe lymphopenia, this risk of bias will probably be minimized as the physician would be expected to perform a closer follow-up with more frequent blood testing. For data sources with additional primary data collection, the data will be entered according to the study protocol and recoding of lymphocyte counts, when performed, is mandatory by the physician. In data sources with secondary use of data, the differences in the recording of lymphocyte counts between different MS treatments and different medical practices will limit the assessment of completeness of recording.

Furthermore, given that oral cladribine is a new drug, the treating physician might pay extra attention and evaluate the patient more frequently (higher number of clinical visits, laboratory testing, etc.), introducing a possible detection bias in comparison to patients treated with fingolimod.

Confounding by indication and/or channeling bias

Confounding by indication and/or channeling bias may result from selective prescribing of a specific medication to patients with a different clinical profile (eg, more severe disease). This bias can also arise because of differences in the contraindications and warning and precaution sections between fingolimod and oral cladribine. This will influence drug prescription and, if related to the outcome, act as a confounding factor.

Oral cladribine will be a new drug coming on the market at the start of this study. Thus, patients newly initiating oral cladribine at the very beginning of the study might be different from patients treated with fingolimod or patients who will be treated in later years (eg, with more comorbidities, lack of treatment responsiveness, particular safety profile, not stabilized with other available MS treatments). This effect is often observed when a new drug enters the market and is known as channeling bias. This effect will tend to decrease upon study course.

To address this potential bias:

- Subgroup analysis restricting the study cohorts to patients with RRMS will give insight on any potential impact of indication on the study results.
- Adjustment of outcomes for confounders and effect modifiers will minimize any differences that are due to the presence of different background risk;
- Propensity score adjustment might be used if the 2 cohorts are shown to have statistically significant key differences in characteristics at enrolment.

Limitations related to data sources

Danish data cannot leave Denmark and must be analyzed on the server of a Danish register holder. This limitation can be overcome by running the pooled analyses on the server of a Danish register holder, where a dedicated virtual server space will ensure secure data storage.

In all Nordic countries, the national healthcare registers have a lag time of 3-12 months. Thus, for example data for the anticipated final study year 2033 will be available during 2034. The study period in the Nordic countries is suggested to end 1 year earlier than for the countries using additional primary data collection, to enable holding the suggested timelines. The target study cohort sizes have been defined across all countries and thus the population sizes to be collected per individual country can be adjusted.

Missing variables

- The OFSEP database in France does not collect data on the date of diagnosis, only on the date of onset.
- Information on race of the patient will not be available.
- Availability of data on the predefined risk factors varies by data source: all variables are not currently available in any of the data sources. However, in the data sources using additional

primary data collection potential missing variables can be collected via a module specifically designed for the study purpose.

9.11 Other Aspects

9.11.1 Independent Ethics Committee

Prior to commencement of the study in the selected participating countries, the study protocol along with other necessary study documentation will be submitted to the relevant Independent Ethics Committee in each country. Permit processes by the other agencies/ regulatory entities might also be required. Information on these processes for considered databases are presented below in Table 5.

Table 5 Permit Processes by Data Source for Considered Registers

Country	Data source	Permit process
Denmark	National registers	Data Protection Agency Data holders
Finland	National registers	Ethics committee Data holders
France	OFSEP	Data holder Data Protection Agency
Germany	NTD	Ethics committee
	MSDS 3D (incl. Spain and Switzerland)	Ethics committee
Italy	Italian MS Registry	Italian Multiple Sclerosis Foundation Ethics committee
Norway	National registers	Ethics committee Data Inspectorate Data holders
Sweden	National registers	Ethics committee Data holder
Australia	MSBase	Data holder Local Ethics committees
Belgium		
Czech Republic		
The Netherlands		
Spain		
Switzerland		
Turkey		
UK		

The study must not start in a country before written confirmation of a favorable approval from the Independent Ethics Committee has been received. Written evidence of favorable approval that clearly identifies the study, and the protocol version reviewed will be issued by the Ethics

Committee and provided to the Sponsor. Submission to an Ethics Committee is not required in Denmark.

Any amendments to the protocol will also be submitted to the concerned Ethics Committee before implementation in the event of substantial changes.

9.11.2 Monitoring

Monitoring will be limited to data monitoring and will be further specified in the Central Data Monitoring Plan.

9.11.3 Health Authorities

The protocol and any applicable documentation (eg, Patient Information and Informed Consent Form) will be submitted or notified to the National Health Authorities in accordance with the regulations of the countries involved in the study.

In the Nordic countries, the protocol will be submitted to the data holders of the selected data sources according to the national regulations and procedures for obtaining person-level data for scientific research.

9.11.4 Quality Assurance

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, or regulatory agencies may conduct quality assurance audits/ inspections at any time during or following a study. The participating data sources must agree to allow auditors/ inspectors direct access to all study-related documents, apart from patient-level data, according to national legislation in participating countries and internal guidelines of the participating databases. The database representative must also agree to allocate his or her time and the time of his or her study staff to the auditors/ inspectors in order to discuss findings and issues.

Before the data delivery to the CRO, the data holders should have collected and managed data according to their own standards. After the data are delivered to the CRO by the data holders, the CRO will process the data and perform basic quality checks.

Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.11.5 Archiving

The archive should be maintained for the period specified by local regulations, where applicable. All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations. In the absence of applicable regulations, the archive should be maintained for at least 5 years after the final study report. In any case, the register holder should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

9.11.6 ENCePP Seal Application

The principal investigator will seek ENCePP Study Seal. The criteria and process for sharing the analytical datasets for third parties are described in Appendix 3 (To be included later).

10 Protection of Human Subjects

Per design, this non-interventional study does not affect the treatment of the patients. The study is conducted by following the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct as well as the Guidelines for GPP. The Sponsor, the CRO, the other participating entities and individuals acting on their behalf commit to adhere to the rules of the ENCePP Code of Conduct in their entirety. The study will be registered into the EU PAS register.

The CRO will receive pseudonymized data including dummy SIDs only. The Sponsor will not have access to the patient level data at any time of the study.

10.1 Subject Information and Informed Consent

In the countries using additional primary data collection, an unconditional prerequisite for a subject's participation in the study is his/her written informed consent. The subject's written informed consent to participate in the study must be given before any study-related activities are carried out.

According to the legislation in each Nordic country, no consent is needed when the data from the national healthcare registers are used for scientific research. However, the data in the Swedish MS registry, the IMSE, and in the Norwegian MS Registry and Biobank are collected with a patient consent.

10.2 Patient Identification and Privacy

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data.

The CRO will maintain information on the study individuals securely on site according to up-to-date standard operating procedures. The CRO will also maintain appropriate data storage, including periodic backup of files, and archiving procedures (see Section 9.11.4). The CRO will comply with procedures that include checking electronic files, maintaining security and data confidentiality, following analyses plans, and performing quality checks for all programs. The Sponsor or other parties outside the CRO cannot receive access to individual-level data. Only aggregated results will be presented to the Sponsor or otherwise published.

11 Management and Reporting of Adverse Events

The management and reporting of adverse events (AEs) varies according to the study model in the country concerned, which can be based on:

- either secondary use of data only,
- or secondary use of data supplemented by primary data collection (mixed model).

According to EU GVP module VI rev 1, non-interventional studies based on secondary use of data (as in the Nordic countries and MSBase) do not require reporting of suspected adverse reactions in the form of Individual Case Safety Reports. Safety data will then be summarised in the interim and final study reports.

In countries where existing registries are supplemented by additional primary data collection, the management and reporting of AEs are described below. In these countries, safety data will mainly be collected via the module specifically designed for the study purpose.

11.1 Adverse Event

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient or clinical study subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

Adverse Reaction (AR)

An AR is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an AE is at least a reasonable possibility.

ARs may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include overdose, abuse, off-label use, misuse, medication error, lack of therapeutic effectiveness.

Reports of Special Situations

- Use of a medicinal product during pregnancy or breastfeeding: reports where embryo, fetus or child may have been exposed to medicinal products (either through maternal exposure or transmission of a medicinal product via semen following paternal exposure)
- Reports of overdose, abuse, off-label use, misuse, medication error or occupational exposure
- Lack of therapeutic effectiveness

- Prescription error/dispensing error, eg, due to confusion of invented names of the medicinal products
- Drug interaction
- Suspected transmission of an infectious agent via a medicinal product
- Product complaints (including falsified product or counterfeit)

Reports of special situation with no associated adverse reaction will not be reported as ICSRs. They will be considered in the study report or any interim reports, as applicable.

Serious Adverse Event (SAEs)/Serious Adverse Reaction (SARs)

A SAE/ SAR is any AE/ AR as defined above, which also fulfills at least one of the seriousness criteria below:

- results in death
- is life-threatening[1)]
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/ incapacity
- is a congenital anomaly/ birth defect
- is otherwise considered as medically important[2)]

[1)] Life-threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

[2)] Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalisation but might jeopardise the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

Any suspected transmission via a medicinal product of an infectious agent is also considered a SAE/ SAR.

Adverse Events of Special Interest (AESI)

An AESI is an AE of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. In this study, severe infections, tuberculosis, PML, other opportunistic infections, malignancies, and severe lymphopenia are considered AESI. AESI should be reported following the procedure described in Section 11.4.

Events Not to be considered as AEs

Medical conditions present in a patient and documented at the time of study enrolment, and that do not worsen in severity or frequency during the study, are defined as baseline medical conditions, and are NOT to be considered as AE.

11.2 Severity of Adverse Events

Investigators should assess the severity/ intensity of any AE as follows:

Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.

Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.

Severe: Significant impairment of functioning: the subject is unable to carry out usual activities.

11.3 Causality Assessment

Investigators must assess the causal relationship between AEs and study drug (including any other non-medicinal product, radiation therapy, etc.) considering temporal relationship between the AE onset and study drug administration, safety profile of study drug (known ARs), the patient's condition (medical history, underlying disease), concomitant medication, and study procedures.

Related: Suspected to be reasonably related to cladribine or fingolimod.

Not related: Not suspected to be reasonably related to any study medication. A reasonable alternative explanation must be provided.

11.4 Recording of Adverse Events

In this study, will be recorded:

- All ARs (ie, events suspected to be related to oral cladribine or fingolimod)
- AESI (severe infections, herpes zoster infection, tuberculosis, PML, other opportunistic infections, malignancies, and severe lymphopenia,) (ie, all such events regardless of the suspected causal relationship to oral cladribine or fingolimod)
- Any fatal cases (ie, all fatal events regardless of the suspected causal relationship to oral cladribine or fingolimod)

In line with the provisions of GVP Module VI rev 1, it can be justified that not all AEs that occur during the course of this PASS need to be collected. Indeed, the known safety profile of oral cladribine has been established based on a large integrated safety data set, including data from

placebo-controlled clinical trials. The majority of AEs are expected to be related to the underlying disease (multiple sclerosis) and would not add meaningful new safety information to the known safety profile of cladribine. As a consequence,

- The main focus of this long-term PASS is to monitor and further characterize the important identified and potential risks of oral cladribine. For these events, AESI will be collected regardless of causal relationship for a 4-year period after treatment initiation.
- In addition, the potential risk of malignancies will be followed for 6 additional years for each patient (so during 10 years in total).
- Furthermore, any AR suspected to be related to cladribine or fingolimod and any fatal cases regardless of causality will be collected during the full study follow-up period (10 years for each patient).

The recording period begins, when the patient is initially enrolled in the study (date of signature of informed consent). Recording will be continued as follows:

- AESI (except malignancies, see below) regardless of causality: 4 years after the enrolment of a patient, which is in line with the SmPC, ie, 2 years treatment in Years 1 and 2 and no further cladribine treatment in years 3 and 4. This period is in line with the duration of cladribine efficacy of at least 4 years.
- AESI of Malignancies (regardless of causality): 10 years after the date of signature of informed consent (duration of the complete patient follow-up)
- ARs: 10 years after the first dose of oral cladribine (duration of the complete patient follow-up)
- Fatal events (regardless of causality): 10 years after the first dose of oral cladribine (duration of the complete patient follow-up)

Each event must be followed until resolution or until the end of the mandatory safety follow-up period of 2 years.

Each SAR, AESI, fatal event, and special situation occurring during the study must be documented by the investigator within 24 hours of awareness and recorded in the safety module* or alternatively a paper form, including:

- description of the event,
- seriousness,
- severity (grading),
- duration (onset and resolution dates),
- causal relationship,
- any other potential causal factors,
- actions taken with the study drug (eg, delay of dosing, withdrawal),

- other action taken,
- medical history,
- concomitant medication,
- required treatment and outcome of the SAR, AESI, fatal event.

*Downloads from the safety module must contain study/site ID, subject ID number; date of birth, gender, and an event description.

Note - *Event term 'Death', 'Disability' and 'Hospitalisation'*

Death, disability, and hospitalization are usually not considered ARs/AEs. Therefore, the primary cause of death, disability or hospitalization should be recorded and reported as an SAE/AR. The outcome of death and disability should be recorded in a separate data field. a term for the outcome will be selected if it is the only information reported or provides significant clinical information.

If death occurs, the primary cause of death or event leading to death should be recorded and reported as a SAE. "Fatal" will be recorded as the outcome of this respective event and not as a separate event. Only, if no cause of death can be identified (for example, sudden death, unexplained death), the death per se may then be reported as a SAE.

Reports of Special Situations (see definition) are also to be recorded according to the SAE procedure in the safety module, even if occurring without AE.

Pregnancy and Breastfeeding. Pregnancy or breastfeeding must be recorded in the safety module and additionally be reported to the Sponsor immediately (within 24 hours of awareness) by using separate paper data collection forms for pregnancy, independent if an AE was reported or not. The outcome of the pregnancy should be followed up and reported to the Sponsor until delivery. In the event of a pregnancy in a participant occurring during the study, the participant must be discontinued from cladribine immediately.

11.5 Safety Reporting to the Study Sponsor

A. Data Sources based on Secondary Use of Data

For data sources based on secondary use of data only (ie, collected for other purposes than this study), predefined safety data will be collected from the database. No safety data collection forms will be used. For studies using this type of data sources, the reporting of suspected adverse reactions to the competent authorities in the form of ICSRs is not required. Reports of (S)ARs/AESI/fatal events/special situations collected will be summarised as part of any interim safety analysis and in the final study report.

B. Data Sources involving Additional Primary Data Collection

For data sources with a combined study design including both primary and secondary data collection, the same requirements as for studies with primary data collection only must be followed. Therefore, the following safety data collection forms are used in this study:

- (Serious) Adverse Event Report Form (or alternatively a qualified electronic data collection and transmission tool, with paper form as back-up)
- Pregnancy Report Form (or alternatively a qualified electronic data collection and transmission tool, with paper form as back-up)
- Parent-Child/Foetus AE Report Form (or alternatively a qualified electronic data collection and transmission tool, with paper form as back-up)
- Adverse Event of Special Interest (AESI) Report Form (or alternatively a qualified electronic data collection and transmission tool, with paper form as back-up). This form is used for non-serious AESI, following the same procedure as for SAE.

Reportable events:

The following events are reportable to the Safety Check Desk at the CRO within 24 hours of awareness:

- Serious AR*
- Fatal cases
- AEs of special interest (AESI)
- Pregnancy or breastfeeding is to be reported by using the Pregnancy Report Form
- All events that occur in a child/ foetus of a pregnant woman who was exposed to the study drug are to be reported by using the Parent-Child/Foetus Report Form
- Special situations (see definition) should be reported on the (Serious) Adverse Event Report Form by indicating whether associated with an adverse event (serious or non-serious).

*All non-serious suspected adverse drug reactions (related to any study medication) only need to be recorded in the EDC. The EDC should fulfill the requirements for qualified electronic data collection. Alternatively, the paper report form will be used.

Procedure for Safety Data Reporting (completion and forwarding):

In the event of any new safety data that have to be reported as specified above, the investigator must immediately (within 24 hours after becoming aware of the event) inform the Sponsor or its designee. For all events that require a written form to the Sponsor, the investigator completes the respective Safety Data Collection Form/ safety module within 24 hours in English and sends the report by email or fax to the CRO Safety Check Desk. The investigator must respond to any request by the CRO for follow-up information, as noted above for initial report and for further forwarding the reports within 24 hours to Global Patient Safety, within the same timeline as noted above. The Sponsor has to meet strict regulatory timelines associated with expedited safety reporting obligations. All non-serious ARs need to be recorded in the EDC, with details as specified above.

The EDC should allow monthly transmission into the Sponsor Global Drug Safety Database. Alternatively, the procedure with paper report forms should be followed.

CRO Safety Check Desk:

- Email: PPD
- Fax: PPD

Global Patient Safety:

- Email: PPD
- Fax: PPD

The data entered on the safety data collection forms/ safety module must be consistent with the information recorded in the country-specific register/ database. If some data are missing, the form should be completed with the available data and a follow-up report will be sent as soon as possible. The minimum information to be included in the initial report is the following:

- Investigator name and contact details
- Subject identification (eg, ID number, gender, age)
- Product (including lot/ batch number)
- Description of SAR/AESI/fatal case/special situation

The report should contain causality and seriousness information (for AEs) and must be signed off/authorized by the investigator.

When AE information is communicated via telephone, a written/ database report must be sent immediately within 24 hours thereafter by fax or e-mail. In such cases, the "clock start" for case reporting to Health Authorities is the date and time of the telephone communication.

Exposure during Pregnancy

All pregnancies with an estimated conception date in the period from the date of informed consent signature (where applicable) until the last post-treatment safety visit, or as defined in the protocol, must be recorded by convention in the AE page/ section of the country specific registry/ database. The same rule applies to pregnancies in female patients and to pregnancies in female partners of male patients. The investigator must notify the Sponsor in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted according to the same process as described for SAE reporting. The Sponsor must be notified about any pregnancy independent whether the pregnancy is associated with an AE or not.

Investigators must actively follow up, document, and report to the Sponsor on the outcome of all these pregnancies and deliveries even if the subject is withdrawn from the study. If an abnormal outcome occurs, the respective safety data collection form (Pregnancy Report Form, Parent-Child/Foetus AE Report Form) is to be completed and sent to the Sponsor. In the event of a

pregnancy in a participant occurring during the study, the participant must be discontinued from oral cladribine immediately.

Procedure for Follow-up Information

The investigator must promptly respond to any request for follow-up information or questions from the Sponsor or delegate (eg, the CRO). Such requests will be sent to the investigator via the CRO Safety Check Desk. ARs, or AESI, fatal cases, or special situations occurring during the study must be monitored and followed up by the investigator until stabilization or until the outcome is known, unless the subject is lost to follow-up.

The investigator will ensure any necessary additional therapeutic measures and follow-up procedures are recorded and reported via a follow-up report form. For all serious cases (including malignancy, severe infections and lymphopenia), missing information such as outcome, confounders, and causality is to be provided. Additionally, follow-up information of non-serious AR may be required by the Sponsor for medical assessment. Reasonable attempts to obtain follow-up information must be made and documented.

Reporting of any new information on a previously reported AR, AESI, fatal case (follow-up), and special situation will follow the procedures and timelines of the original report.

11.6 Regulatory Reporting to the Health Authorities

A. Secondary Use of Data

No reporting in form of ICSRs is required.

B. Primary Data Collection

Expedited reporting of serious and non-serious AR to Competent Authorities/ EMA is performed by the Sponsor according to applicable global and local requirements.

In addition, the investigator will comply with any applicable local pharmacovigilance requirements to report appropriate safety data, to national pharmacovigilance systems (eg, Yellow Card Scheme in UK), as required by country specific reporting requirements. The Investigator will inform the Sponsor of any such reporting.

12 Plans for disseminating and communicating study results

12.1 Study Report

Five study reports are planned:

- Full interim report after 3 years (after start of data collection)
- Full interim report after 6 years (after start of data collection)

- Full interim report after 9 years (after start of data collection)
- Full interim report after 12 years (after start of data collection)
- Final report after study completion (the study will be completed 15 years after initiation).

All reports will accurately and completely present the study objectives, methods, results, limitations of the study, and interpretation of the findings. Study reports will present the number and proportion of enrolled patients in each cohort per participant country. A summary of all ARs will be provided in all interim reports and the final study report.

The final study report will be submitted to the Health Authorities, at the latest within a year after end of data collection. Please see Section 6, Milestones, for timing of interim and final reports.

12.2 Publication

Based on the study report, the principal investigator and co-investigators (together referred to as "investigators"; members of the responsible parties and possible other contributors approved by the responsible parties) will prepare (a) scientific manuscript(s) for academic publication. The responsible parties decide the publication forums.

The investigators will inform the Sponsor in advance about any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc), either in whole or in part, by investigators or their representatives will require pre-submission review and approval by the Sponsor.

The principal investigator and the Sponsor are committed to ensuring that authorship for all publications should comply with the criteria defined by the International Committee of Medical Journal Editors, ICMJE. It is stated that each author should have participated sufficiently in the work to take public responsibility for the content. These conditions apply equally to external investigators and to employees of the Sponsor.

Within 3 months following the study report, an abstract of the study findings will be made available to the public through the EU PAS register. According to the ENCePP Code of Conduct, the principal investigator is responsible for publication of the results. The main results of the study will be published, whether positive or negative, including results from a possibly prematurely terminated study. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests. The Sponsor is entitled to view the final results and interpretations prior to submission for publication in the EU PAS register, and to comment these without unjustifiably delaying the publication. The Sponsor will maintain the right to delay publication in order to protect intellectual property rights. The principal investigator may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period due to pending response from the peer-review process.

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14 Appendices

14.1 List of Stand-Alone Documents

Number	Document reference number	Date	Title
1	Version 2.0	27.02.2018	Steering Committee Charter

14.2 ENCePP Checklist for Study Protocols

Doc.Ref. EMA/540136/2009

European Network of Centres for Pharmacoepidemiology and Pharmacovigilance

ENCePP Checklist for Study Protocols (Revision 3)

Adopted by the ENCePP Steering Group on 01/07/2016

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorisation holders when submitting the protocol of a non-interventional post-authorisation safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorisation safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine − CLARION

Study reference number: MS 700568-0002

Section 1: Milestones		Yes	No	N/A	Section Number
1.1	Does the protocol specify timelines for				
	1.1.1 Start of data collection1	☒	☐	☐	6
	1.1.2 End of data collection2	☒	☐	☐	6
	1.1.3 Study progress report(s)	☒	☐	☐	6
	1.1.4 Interim progress report(s)	☒	☐	☐	6
	1.1.5 Registration in the EU PAS register	☒	☐	☐	6
	1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question		Yes	No	N/A	Section Number
2.1	Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	9.2.2
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
	2.1.5 If applicable, that there is no a priori hypothesis?	☐	☐	☒	

Comments:

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

2 Date from which the analytical dataset is completely available.

Section 3: Study design		Yes	No	N/A	Section Number
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, new or alternative design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.2
3.3	Does the protocol specify measures of occurrence? (e.g. incidence rate, absolute risk)	☒	☐	☐	8
3.4	Does the protocol specify measure(s) of association? (e.g. relative risk, odds ratio, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	9.8.3
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		Yes	No	N/A	Section Number
4.1	Is the source population described?	☒	☐	☐	9.2.1
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period?	☒	☐	☐	9.2.4
	4.2.2 Age and sex?	☐	☒	☐	
	4.2.3 Country of origin?	☒	☐	☐	9.2
	4.2.4 Disease/indication?	☒	☐	☐	9.2.2
	4.2.5 Duration of follow-up?	☒	☐	☐	9.2.4
	4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.1.1

Comments:

Section 5: Exposure definition and measurement		Yes	No	N/A	Section Number
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.2.3 9.4.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3	Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	9.4.1
5.4	Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	

Comments:

Section 6: Outcome definition and measurement		Yes	No	N/A	Section Number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	9.1.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.4.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☐	☒	☐	
6.4	Does the protocol describe specific endpoints relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease, disease management)	☐	☒	☐	

Comments:

	Section 7: Bias	Yes	No	N/A	Section Number
7.1	Does the protocol describe how confounding will be addressed in the study?	☒	☐	☐	9.10
	7.1.1. Does the protocol address confounding by indication if applicable?	☒	☐	☐	9.10
7.2	Does the protocol address:				
	7.2.1. Selection biases (e.g. healthy user bias)	☒	☐	☐	9.10
	7.2.2. Information biases (e.g. misclassification of exposure and endpoints, time-related bias)	☒	☐	☐	9.10
7.3	Does the protocol address the validity of the study covariates?	☐	☒	☐	

Comments:

	Section 8: Effect modification	Yes	No	N/A	Section Number
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.3.3 9.8.3

Comments:

	Section 9: Data sources	Yes	No	N/A	Section Number
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.5
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.5
	9.1.3 Covariates?	☒	☐	☐	9.5
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3
	9.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3

Section 9: Data sources	Yes	No	N/A	Section Number
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Appendix 1
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD)-10, Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Appendix 1
9.3.3 Covariates?	☒	☐	☐	Appendix 1
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.7.2

Comments:

Section 10: Analysis plan	Yes	No	N/A	Section Number
10.1 Is the choice of statistical techniques described?	☒	☐	☐	9.8
10.2 Are descriptive analyses included?	☒	☐	☐	9.8.3
10.3 Are stratified analyses included?	☒	☐	☐	9.8.3
10.4 Does the plan describe methods for adjusting for confounding?	☒	☐	☐	9.8.3
10.5 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8.2
10.6 Is sample size and/or statistical power estimated?	☒	☐	☐	9.6

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Section Number
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.7
11.2 Are methods of quality assurance described?	☒	☐	☐	9.7 9.11.4
11.3 Is there a system in place for independent review of study results?	☐	☐	☒	

Comments:

Section 12: Limitations	Yes	No	N/A	Section Number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.10
12.1.2 Information bias?	☒	☐	☐	9.10
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒	☐	☐	9.10
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☒	☐	☐	

Comments:

Section 13: Ethical issues	Yes	No	N/A	Section Number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.11.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Section Number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

Section 15: Plans for communication of study results		Yes	No	N/A	Section Number
15.1	Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2	Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the main author of the protocol: PPD

Date: 19/06/2018

Signature PPD

14.3 Additional Information

Appendix 1. Variable definitions (to be included)

Appendix 2. Descriptions of data sources

Appendix 3. ENCePP Study Seal

14.4 Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine - CLARION
Study Protocol Date / Version:	19 June 2018/ Version 1.9

Protocol Lead responsible for designing the non-interventional study:

I approve the design of the non-interventional study protocol:

PPD _____ PPD

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250 64293 Darmstadt, Germany
Telephone number:	PPD
E-mail address:	

Signature Page – EU QPPV

Study Title:	Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine - CLARION
Study Protocol Date / Version:	19 June 2018/ Version 1.9

EU QPPV, European Union Qualified Person responsible for Pharmacovigilance:

I approve the design of the non-interventional study:

PPD PPD

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	
Institution:	Merck KGaA
Address:	Frankfurter Strasse 250 64293 Darmstadt, Germany
Telephone number:	PPD
Fax number:	
E-mail address:	

Signature Page – Principal Investigator

Study Title	Long term, prospective, observational cohort study evaluating the safety profile in patients with highly active relapsing multiple sclerosis (RMS) newly started on oral cladribine - CLARION
Study Protocol Date / Version	19 June 2018/ Version 1.9

Principal Investigator

I, the undersigned, am responsible for the conduct of the study at this site and affirm that I understand and will conduct the study according to the study protocol, any approved protocol amendments, Good Pharmaco-epidemiology Practices (GPP) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of the study to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

PPD PPD

Signature Date of Signature

Name, academic degree:
Function / Title:
Institution:
Address:
Telephone number:
Fax number:
E-mail address:

PPD

Appendix 1 Variable definitions

To be included.

Appendix 2 Descriptions of data sources

This appendix describes the multiple data sources (registries, databases and registers) which have been selected and will be used for this PASS. Only countries with existing data sources with capability for secondary collection of data or additional primary collection of data were eligible for inclusion in this study.

MSBase – Multi-countries

MSBase is a longitudinal observational MS database open to all practicing neurologists and their team worldwide. Data collection has started in September 2003. MSBase includes also a web-based platform dedicated to sharing, tracking and evaluating outcomes data in MS and other CNS demyelinating diseases. The database contains information such as clinical evaluation of patients, laboratory measurements (including lymphocyte counts) and the drugs used to treat MS. Prior to the initiation of this study, a feasibility study was performed to aid selection of participating European countries in MSBase. Some countries did not participate in MSBase (Austria, Germany, Finland, France, Ireland, Norway, Poland, Portugal, Slovakia, and Sweden). Among those that reported data to MSBase, additional countries were excluded due to 1) existence of another country registry that had broader coverage and with overlapping centers (e.g., Denmark: Danish MS Register), or 2) low number of patients with at least one visit entered in MSBase (e.g., Greece, Hungary). The countries finally selected for this study are: Belgium, Czech Republic, the Netherlands, Spain, Italy, Switzerland, Turkey, and the United Kingdom. In each center, the principal investigator of the site decides participation to different studies. All the patients in the database have signed a consent. The permit processes, including ethical approvals, are coordinated with the site principal investigators.

OFSEP - France

Up to 2013, OFSEP was based on an existing cohort of MS patients in France. Today the data are collected from participating centers using the European Database for Multiple Sclerosis (EDMUS) software. OFSEP covers approximately 50% of the total MS population in France and has data for approximately 55,000 patients in total. Of these, 23,000 patients have records after June 2013. OFSEP contains information such as clinical evaluation of patients, the drugs used to treat MS, results of magnetic resonance imaging (MRI) and blood sample analyses (including lymphocyte counts). Access to the data is made directly via an application to the database: the National Coordination Center and the Scientific Board of the database evaluate the applications and the Steering Committee makes the final decision.

NTD - Germany

The NTD database has been established in February 2008, with data collection from 73 practices across Germany. At the moment the database covers approximately 25,000 MS patients. NTD

contains data on the demographic, clinical and socio-economic parameters of the MS patients, recorded at least once per quarter Additional primary data collection can be implemented, and data is entered according to the study protocol. The recoding of all study variables (including lymphocyte counts) is mandatory by the physician ensuring high data quality and completeness. In general, the NTD database has an existing ethical approval, but new studies utilizing the NTD data need a separate ethical approval. The application process is managed by the local principal investigator.

MSDS 3D – Germany, Spain and Switzerland

The MSDS 3D database has been established in 2010. As the database is solely used for conducting specified studies, the number of practices and patients varies by study. For example, in the PANGAEA study studying fingolimod users across Germany recruited approximately 4,000 RRMS patients from approximately 500 neurological centers. MSDS 3D contains information such as clinical evaluation of patients, the drugs used to treat MS and results of MRI. Patient-reported outcomes are also available. Additional primary data collection can be implemented, and data is entered according to the study protocol. The recoding of all study variables (including lymphocyte counts) is mandatory by the physician ensuring high data quality and completeness. The application processes are managed by the local principal investigator.

Italian MS Registry - Italy

The Italian MS Registry includes data from 57 practices across Italy. This database is managed by the hospital of Bari. The 57 centers cover approximately 80% of the Italian MS population. The database utilizes iMED software, the same as MSBase and contains information such as clinical evaluation of patients, laboratory measurements (including lymphocyte counts) and the drugs used to treat MS.

Finland

Each individual permanently residing in Finland (at least for 1 year) has a unique personal identity number (PID), which carries also information on date of birth and gender. All the data sources listed below include information PIDs that enable linkage of data from different data sources.

Finnish MS data collection system

Finnish MS data collection system is established by a Finnish company called StellarQ. This company acts as a data solution provider for 13 of the 20 Finnish hospital districts and all public healthcare units of these hospital districts treating MS patients utilize their software. The database was established in 2014, but retrospective data collection have been extensively conducted in most hospital districts. The work is still ongoing. The database covers all the major hospital districts treating MS patients in Finland. The database contains extensive and detailed data on the MS patients with additional automatic data extractions from the laboratory databases (including lymphocyte counts) of the contributing hospitals. The data are updated real-time. The hospital districts providing the data to the database are the data holders and permits to obtain access to the data need to be applied separately from each hospital district.

Prescription registers

In Finland, there are 2 different prescription registers: the traditional Prescription register and the new e-Prescription register. The Prescription register is managed by the Social Insurance Institute and contains data since 1994. The e-Prescription register is held by Social Insurance Institute but managed by the National Institute for Health and Welfare. Use of e-prescriptions has been compulsory in public health care since April 2013, and in private health care since January 2015. e-Prescription register is not replacing the traditional Prescription register but they both are further in use. The functions are partly overlapping.

The Prescription register covers prescribed, purchased and reimbursed medication, while the e-Prescription register covers all prescribed and purchased medication. Otherwise the data contents are similar: information on eg, date of purchase, and trade name, Anatomical Therapeutic Chemical (ATC) code, strength and package size of the drug. In both registers, data for previous year are available for research purposes in March. Access to the data for scientific research through a standard application procedure is applied from Social Insurance Institute for the Prescription register and from the National Institute of Health and Welfare for the e-prescription register.

Care Register for Health Care (HILMO)

Care Register for Health Care is managed by the National Institute for Health and Welfare. It contains data since 1994. This national register covers virtually 100% of the Finnish population (5.5 million in 2017). The data consist of information on secondary care (in- and outpatient care) details, eg, duration of hospitalization, diagnoses (ICD-10 codes) and medical procedures.

Detailed information is available on in-patient care at psychiatry specialty and on patients with an advanced cardiac condition. The quality of the data is considered mainly very high, but there is variation, eg, in the secondary diagnoses' reporting rate and accuracy (personal communication with the register, 2016). Data for previous year are available for research purposes in September. Access to the data for scientific research is applied from the National Institute of Health and Welfare through a standard application procedure.

Register of Primary Health Care Visits (AvoHILMO)

Register of Primary Health Care Visits is managed by the National Institute for Health and Welfare. This national register covers virtually 100% of the Finnish population (5.5 million in 2017) since 2011. In this register, information about primary health case visits, eg, time and place of treatment as well as diagnoses (ICD-10 codes) and procedures, are recorded. The reliability and accuracy of the reported data has increased since the establishment of this register. The lag time of the data availability is similar to the HILMO register. Access to the register data for scientific research is applied similarly than for the HILMO data, via the National Institute of Health and Welfare.

Finnish Cancer Registry

Finnish Cancer Registry has data since 1953, and is currently managed by the National Institute for Health and Welfare. It contains information eg, on the time of diagnosis, topography and morphology of the tumor, and the type of the primary treatment given within 4 months of diagnosis. Lag time of the data availability for scientific research is approximately 1.5 years.

National Infectious Diseases Register

The Finnish National Infectious Diseases Register is managed by the National Institute for Health and Welfare, and has data since 1995. All laboratories and doctors are mandated by law to report diagnosed communicable diseases caused by 70 specified pathogens (eg, HIV infection and tuberculosis) into the National Infectious Diseases Register. The register contains details such as pathogen, basis of diagnosis and course of the infection. Access to the register data for scientific research is applied from the National Institute of Health and Welfare through a standard application procedure.

Cause of Death Register

In Finland, Cause of Death Register is managed by Statistics Finland. Data in electronic form are available since 1969. Reporting rate is virtually 100%. The information recorded includes cause of death (ICD-10 codes have been used since 1998) and time of death. Complete cause of death statistics for the year before previous year are available in January (eg, data for 2016 are available in January 2018). Time of death is, however, available at the end of the year. Access to the register data for scientific research is applied from Statistics Finland through a standard application procedure.

Sweden

Each registered resident in Sweden has a unique PID, if the residency has lasted or is expected to last for at least 1 year. The PID carries information on the date of birth and gender. All the data sources listed below have information on this unique personal identification number enabling linkage of the different data sources.

Swedish MS Registry

Swedish MS Registry, with data from 1996 onwards, has been established in 2001. Since 2011 it has been part of the Swedish Neuro Registries. On national level, approximately 82% of the Swedish MS patients were included in the register in 2016 (coverage between counties varying between 62 and 92%). This coverage has been steadily growing. The register includes detailed data on Swedish MS patients, with data on eg, characteristics of the MS disease, laboratory measurements (including lymphocyte counts) and MS treatment. Access to the register data for scientific purposes is applied directly from the register through a standard application procedure.

In Sweden, a post-marketing surveillance system, IMSE (Immunomodulation and MS epidemiology) has been in use since 2006, effectively recording efficacy, treatment switches, as well as major adverse events, together with biobanked biological samples allowing follow up studies of unexpected adverse events handled through the web-based Swedish MS registry. The Swedish MS society therefore aims to enter all new MS drugs into this system. The biobanked material has already proven very useful in that it has enabled a retrospective assessment of JCV serology in the Swedish population treated, providing a way to stratify the risk for persons receiving the treatment.

Swedish Prescribed Drug Register

National Swedish Prescribed Drug Register, managed by the National Board of Health and Welfare, covers virtually 100% of the Swedish population (10 million in 2017). This register has data since 2005. It contains information on all prescribed medicines dispensed by community pharmacies, eg, date of prescribing and dispensing, and trade name, ATC code, strength and package size of the drug. Prescribed dose and indication are, however, available only if as an optional free-text instruction to the patient. The data is updated monthly. Access to the register data for scientific research is applied from the National Board of Health and Welfare through a standard application procedure.

National Patient Register

The Swedish National Patient Register, managed by the National Board of Health and Welfare, covers virtually 100% of the Swedish population (10 million in 2017). This register has data since 1987. It covers all inpatient care since 1987 and special outpatient care from 2001 onwards. Primary care data is not included in this register. Recorded variables include eg, discharge diagnoses (ICD-9 or -10 codes) and performed medical procedures. Currently the National Patient Register is updated monthly. Access to the register data for scientific research is applied from the National Board of Health and Welfare through a standard application procedure.

Swedish Cancer Registry

Swedish Cancer Registry has data since 1958. It contains information on eg, date of diagnosis and details of the tumor (site, histological type and stage), but not on treatment. Data for the year before previous year are available in January (eg, data for 2016 are available in January 2018).

Cause of Death Register

The Cause of Death register has data since 1953. The information recorded includes eg, cause of death (ICD-10 codes have been used since 1998), time of death, and intention in cases of injury or poisoning. The reporting rate is virtually 100%. Data for previous year are available in August. Access to the register data for scientific research is applied from the National Board of Health and Welfare through a standard application procedure.

Norway

Each permanent resident (staying at least for 6 months) in Norway has a unique PID that carries information on the date of birth and gender. All the data sources listed below include information on PIDs that enables linkage of data from different sources.

Norwegian MS Registry and Biobank

The Norwegian MS Registry and Biobank has been established in 2001. On national level, approximately 55% of the Norwegian MS patients are included in the register. The register includes detailed data on the MS patients, with data on eg, characteristics of the disease as well as the treatment and laboratory measurements (including lymphocyte counts). Access to the register data for scientific research is applied directly from the register through a standard application procedure.

Norwegian Prescription Database

Norwegian Prescription Database is managed by the Norwegian Institute of Public Health and it contains data since 2004. This national register covers virtually 100% of the Norwegian population (5.2 million in 2017). The data cover all prescribed drugs dispensed at pharmacies. Drugs used in hospitals and institutions are not recorded in this register. The Norwegian Prescription Database contains information on eg, date of purchase, trade name, ATC code, strength, and package size of the drug. Data for previous year are available in April. Access to the register data for scientific research is applied from the Norwegian Institute of Public Health through a standard application procedure.

Norwegian Patient Registry

Norwegian Patient Registry is managed by the Norwegian Directorate of Health. This national register has data since 2008 and it covers virtually 100% of the Norwegian population (5.2 million in 2017). It contains information on patients who have been referred to hospital treatment but are still on a waiting list for treatment, or who have been treated at hospital, medical outpatients' clinic or at contract specialist clinic. The data cover hospitalization details such as diagnoses (ICD-10 codes) and medical procedures. Lag time in data availability is approximately 3 to 6 months. Access to the data for scientific research is applied from the Norwegian Directorate of Health through a standard application procedure.

Cancer Registry of Norway

Cancer Registry of Norway is managed by Oslo University Hospital Trust, and it contains data since 1951. Recorded data consist of eg, tumor characteristics (site, topography, morphology, metastatic status, stage) as well as of medical procedures performed and type of treatment given. Data for previous year are available in December. Access to the register data for scientific research is applied from the register holder through a standard application procedure.

Cause of Death Registry

The Cause of Death Registry is managed by the Norwegian Institute of Public Health, and it has data since 1951. The main variables recorded in this register are cause of death (ICD-10 codes) and time of death. The reporting rate virtually 100%. Data for previous year are available in November. Access to the register data for scientific research is applied from the Norwegian Institute of Public Health through a standard application procedure.

Denmark

Each individual residing permanently (at least for 3 months) in Denmark has a unique PID, which carries information on the date of birth and gender. All the data sources listed below include information on PIDs that enables linkage of data from different sources.

Danish Multiple Sclerosis Registry and the Danish MS Treatment Register

The Danish Multiple Sclerosis Registry (DMSR) including data from 1948 onwards was formally established in 1956. It is compulsory for all health care departments treating MS patients to provide

data to this register. The DMSR contains detailed data at the time of diagnosis, e.g., of the symptoms and clinical tests (including lymphocyte counts). No follow-up data are available, except for survival. The DMSR is combined with the Danish MS Treatment Register (DMSTR) which includes data on all patients with disease-modifying treatments since 1996, and providing data to this register is compulsory as well. The DMSTR includes detailed data on drug treatments, with follow-up data on eg, relapses, side effects and disease progression during medication.

The combined register is currently preparing a safety module to be added to the database. It is also possible to add new variables to the register, increasing the value of data captures. Access to the DMSR and DMSTR data for scientific research can be applied directly to the register.

Registry of Medicinal Products Statistics

Registry of Medicinal Products Statistics, managed by the Danish Health Data Authority, covers virtually 100% of the Danish population (5.7 million in 2017). The register has data since 1995. Data on all prescribed medication dispensed from community pharmacies are available. The registry contains information on date of purchase, trade name, ATC code, defined daily dose of the drug, as well as number of purchased packages. Prescribed dose and indication are, however, available as an optional free-text instruction to the patient.

In this national register, data are updated twice a year. Data from January to June are usually available in August the same year, and data from July to December in February the following year. Access to the registry data for scientific research is applied from the Danish Health Data Authority through a standard application procedure. The Applicant must be a Danish public research organization. It is not allowed to transfer individual-level data from the server of the Danish Health Data Authority. This means that all analyses using data from this registry (with or without linked data from other data sources) must be conducted at the server of this authority.

National Patient Register

National Patient Register, managed by the Danish Health Data Authority, covers virtually 100% of the Danish population (5.7 million in 2017) admitted to somatic hospitals, emergency rooms, and specialty outpatient clinics (secondary care) in Denmark. This register has data on admissions to hospitals since 1977, and on admissions to emergency rooms and outpatient clinics since 1995. Data from primary care and psychiatric care are not included in the National Patient Register.

The National Patient Register contains information on hospitalization details such as type of treatment, and diagnoses and operations in secondary care. Data for the previous year are usually available in March. Access to the register data for scientific research is applied from the Danish Health Data Authority through a standard application procedure. The Applicant must be a Danish public research organization.

Danish Cancer Registry

Danish Cancer Registry has data since 1943 including all incident malignant neoplasms (and certain precancerous and benign lesions) with information on eg, date of diagnosis and tumor characteristics (morphology, topography, behavior, stage). Data for the year before previous year are available in January (eg, data for 2016 are available in January 2018).

Danish Register of Causes of Death

Danish Register of Causes of Death, managed by the National Board of Health, has data since 1968. It contains information on time and cause of death, and on post-mortem examinations. The reporting rate is virtually 100%. Data for the year before previous year are available in the beginning of the year (eg, data for 2016 are available in the beginning of 2018). Access to the register data for scientific research is applied from the Norwegian Directorate of Health through a standard application procedure.

Appendix 3 ENCePP Study Seal

Sharing of study data

Access to the study data cannot be given to any third parties, and the study data cannot be used for other purposes than described in this protocol. This is due to data privacy regulations and terms of the data permits granting access to the data. All requests to use the study data for other purposes than mentioned in this study protocol must be subjected to appropriate data permit processes.