Non-Interventional Study Protocol

Study Protocol Number	MS700568_0070
Title	Oral CLADribine in patients that Change from first-line Disease Modifying Treatments for Multiple Sclerosis: a pROspective effectivenesS and Safety study (CLAD CROSS)
Protocol version identifier	2.0
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Replaces Version	v1.1
Active substance	Cladribine
Medicinal product	Cladribine tablets

Sponsor	Merck Hellas sa. 41-45 Kifisias Avenue, 15123 Marousi, Athens, Greece Sponsor Legal Representative in the European Union Merck Healthcare KGaA, Darmstadt, Germany, an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Strasse 250 64293 Darmstadt, Germany
Research question and objectives	The main aim is to study in the real world setting the effectiveness of Cladribine tablets in terms of ARR (Annualized Relapse Rate) and disability progression, in patients who switch from a first line DMD (Disease Modifying Drug) (Interferons, Glatiramer Acetate, Teriflunomide, DMF (Dymethyl fumarate)). **Primary Objective:** • To study the change in annualized relapse rate (ARR) in patients switching from first-line DMDs to Cladribine tablets, between the 12-month pre-baseline period and over the 12 months period before End of Study follow-up (2 years) **Secondary Objectives:** • To assess change in annualized relapse rate (ARR) in patients switching from first-line DMDs to Cladribine tablets, between the 12-month pre-baseline period and over the 12 months period after initiation of Cladribine tablets (1 year) • To assess disability progression [1] • To assess disability improvement [1] • To assess safety of Cladribine tablets in the real world setting, at two years • To assess Quality of Life and treatment satisfaction

[1] Disability progression is defined as progression on ≥1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ≥24 weeks apart and with a ≥20% minimum threshold change for T25FW and 9HPT. Progression on EDSS is defined as at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score is 0. Disability Improvement is defined as improvement on ≥1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ≥24 weeks apart and with a ≥20% minimum threshold change for T25FW and 9HPT. Improvement on EDSS is defined as a decrease in EDSS by at least 1 point (1.5 points if baseline EDSS was 1.5). T25FW and 9HPT are optional and will be performed if done as per routine practice.

- To assess treatment adherence
- CCI [redacted]

Countries of study EMEA Countries (Europe, Middle East and Africa)

Author

PPD [redacted]
PPD [redacted]
PPD [redacted]
[redacted]
Postode: PPD [redacted]
[redacted]
Phone: PPD [redacted]
Fax: PPD [redacted]
E-mail PPD [redacted]

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2 List of Abbreviations

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AR	Adverse Reaction
ARR	Annualized Relapse Rate
CI	Confidence Intervals
CNS	Central Nervous System
CUA	Cumulative Unique Active
CRF	Case Report Form
CRO	Contract Research Organization
DMD	Disease Modifying Drug(s)
DMF	Dymethyl Fumarate
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GA	Glatiramer Acetate
GP	General Practitioner
GVP	Good Pharmacovigilance Practices
HCP	Healthcare Provider
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IFN	Interferon
INN	International Nonproprietary Name
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MRI	Magnetic Resonance Imaging

MS	Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
RMP	Risk Management Plan
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
USA	United States of America
TARB	Therapeutic Area Review Board
TSQM	Treatment Satisfaction Questionnaire for Medication

3 Responsible Parties

Responsible Parties	Contact details
Coordinating (Primary) Investigator (PPD	PPD Phone: PPD E-mail PPD
Protocol Lead	PPD Phone: PPD E-Mail PPD
RCO Lead	PPD Phone: PPD E-Mail: PPD

3.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the study at his/her site. He/She 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 investigators. Accordingly, the Investigator 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. Subsequently, if the prescribed treatment is in line with the study protocol, the Investigator will consider the possibility of including the patient in the study.

The Investigator is responsible for adverse reaction and/or laboratory abnormalities recording and reporting, as specified in Section 11.

4 Abstract

Title	Oral CLADribine in patients that Change from first-line Disease Modifying Treatments for Multiple Sclerosis: a pROspective effectivenesS and Safety study (CLAD CROSS)
Rationale and background	Recently, the number of available disease-modifying therapies for treatment of relapsing-remitting MS (RRMS) has increased. However, many patients treated with these agents continue to experience relapses and disease progression. Cladribine is a synthetic deoxyadenosine analog that acts in peripheral tissues, enters the CNS and is taken up by lymphocytes and phosphorylated by deoxycytidine kinase, resulting in targeted and sustained reductions of the T and B lymphocytes. In the Phase III CLARITY study treatment with Cladribine tablets given in short courses annually for 2 years significantly improved clinical and MRI outcomes. In the Phase III ORACLE-MS study, Cladribine significantly reduced the risk of clinically definite MS in patients with a first clinical demyelinating event compared with placebo. **Study Rationale:** The main aim is to study in the real world setting the effectiveness of Cladribine in terms of ARR and disability progression, in patients that switch from a first-line drug (Interferons, Glatiramer Acetate, Teriflunomide, DMF). The Phase III ONWARD study has shown a significant reduction in ARR when comparing the pre-baseline treatment period with the Cladribine tablets treatment period. However, the study allowed all IFNs as pre-baseline treatments and pooled them together in the analysis. It was also not powered to detect differences in ARR and it did not include other first line treatments (DMF and Teriflunomide) in the analysis. In the current study we want to evaluate the potential reduction in ARR associated with Cladribine tablets treatment, compared to the pre-baseline period, in patients receiving first-line disease-modifying drugs, who switch to Cladribine tablets according to the decision of their treating physician.
Research question and objectives	The main aim is to study in the real world setting the effectiveness of Cladribine tablets in terms of ARR and disability progression, in patients who switch from a first-line disease modifying drug (Interferons, Glatiramer Acetate, Teriflunomide, DMF). **Primary Objective:** • To study the change in annualized relapse rate (ARR) in patients switching from first-line DMDs to Cladribine tablets, between the 12-month pre-baseline period and over the 12 months period before End of Study follow-up (2 years)

	Secondary Objectives: • To assess change in annualized relapse rate (ARR) in patients switching from first-line DMDs to Cladribine tablets, between the 12-month pre-baseline period and over the 12 months period after initiation of Cladribine tablets (1 year) • To assess disability progression. Disability progression is defined as progression on ⩾1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ⩾24 weeks apart and with a ⩾20% minimum threshold change for T25FW and 9HPT. T25FW and 9HPT are optional and will be performed if done as per routine practice. Progression on EDSS is defined as at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score is 0. • To assess disability improvement. Disability Improvement is defined as improvement on ⩾1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ⩾24 weeks apart and with a ⩾20% minimum threshold change for T25FW and 9HPT. T25FW and 9HPT are optional and will be performed if done as per routine practice. Improvement on EDSS is defined as a decrease in EDSS by at least 1 point (1.5 points if baseline EDSS was 1.5). • To assess safety of Cladribine tablets in the real world, at two years • To assess Quality of Life and treatment satisfaction • To assess treatment adherence • CCI [redacted]
Study Design	This is a prospective, non-interventional, multicenter, Phase IV study in patients with a confirmed diagnosis of RRMS who switched from first-line DMDs (Interferons, Glatiramer Acetate, Teriflunomide, DMF) to treatment with Cladribine tablets in routine clinical practice.
Population	**Inclusion Criteria:** 1. Patients must voluntarily give written informed consent. Patients must read and fully understand the Informed Consent Form (ICF) 2. Adult patients, Male or female patients ≥ 18 years old

	3. Patients with confirmed diagnosis of Relapsing-Remitting Multiple Sclerosis (RRMS) diagnosed by the treating physician according to applicable clinical practice guidelines (currently McDonald 2017 criteria), with high disease activity. 4. Patients should have been treated with the same first-line DMD (Interferons, Glatiramer Acetate, Teriflunomide, DMF) and at a stable dose for at least one year prior to switch to Cladribine tablets and should have been prescribed Cladribine tablets according to the decision of the treating physician and for any reason deemed necessary, prior to enrollment in the study. Any washout period and/or washout methods required before switching (such as elimination of Teriflunomide) must have been conducted, according to the decision of the treating physician. 5. Required history data should be available: - MS data for the 12-months pre-baseline period (annualized relapse rate) - MS Medication History (prior DMDs) 6. Fulfilment of the indication for treatment with Cladribine tablets per standard of care in accordance with the local SmPC **Exclusion criteria**: Patients are not eligible for this study if they fulfill any of the following exclusion criteria: 1. Contraindications to use of cladribine tablets according to the Summary of Product Characteristics 2. Patients with history of alcohol or drug abuse that could potentially interfere with their participation in the study. 3. Patient that have received Cladribine in the past 4. Concurrent participation in an investigational study in which patient assessment and/or treatment may be dictated by a protocol
Outcomes	**Primary Endpoint** Difference in ARR between the pre-baseline 12-month period and over the 12 months period before End of Study follow-up (2 years). **Secondary Endpoints** • Difference in ARR between the pre-baseline 12-month period and over the 12 months period after start of cladribine (1 year)

	• Percentage of patients with 6-month disability progression (EDSS, T25FW, 9-HPT)[2] at the end of the study follow-up period (2 years). • Percentage of patients with 6-month disability improvement (EDSS, T25FW, 9-HPT)[2] at the end of the study follow-up period (2 years). • Occurrence of adverse events and of serious adverse events. • Quality of life (MSIS-29), Treatment Satisfaction (TSQM v1.4) and CCI [redacted] • Treatment adherence, assessed as percentage of cladribine tablets taken versus prescribed dose
Variables	• Demographics • Medical History • MS history • Prior and current MS medication • Reason for switching from first line DMD to Cladribine tablets • Therapy with Cladribine Tablets (date of administration and number of tablets taken versus prescribed dose) • Participation in a Cladribine Patient Support Program • Relapse Count: ARR • Disability test: EDSS, Timed 25-Foot Walk, 9-Hole Peg Test (EDSS Plus) • Quality of life questionnaire: MSIS-29 • CCI [redacted] • Treatment Satisfaction Questionnaire: TSQM v1.4

[2] Disability progression is defined as progression on ≥1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ≥24 weeks apart and with a ≥20% minimum threshold change for T25FW and 9HPT. Progression on EDSS is defined as at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score is 0. Disability Improvement is defined as improvement on ≥1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ≥24 weeks apart and with a ≥20% minimum threshold change for T25FW and 9HPT. Improvement on EDSS is defined as a decrease in EDSS by at least 1 point (1.5 points if baseline EDSS was 1.5). T25FW and 9HPT are optional and will be performed if done as per routine practice.

	• Safety [Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESI) and Adverse Drug Reactions (ADRs)]
Data Sources	Data will be collected via an electronic case report form ((e)-CRF). In addition, paper questionnaires will be completed by the subject and then will be transferred into the (e)-CRF.
CCI	242 patients with confirmed diagnosis of Highly Active Relapsing-Remitting Multiple Sclerosis (RRMS) will be enrolled in the participating countries. CCI [redacted]
Data Analysis	All endpoints will be presented by descriptive statistics for Baseline, 12-month, and End of Study assessments. Assessments done at 6-month and 18-months will be presented similarly. Quantitative (continuous) variables will be summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), median, min-max, Q1-

	Q3]. Qualitative (categorical) variables will be displayed as frequencies and percentages (N, %). The normality of distributions will be examined using the Shapiro-Wilk test in order to determine whether or not to use parametric methods for analysis. **Primary Endpoint:** Pre- and post-baseline ARR (2 years) will be compared by ANOVA or Wilcoxon signed-rank test if data is not normally distributed. The 95% Confidence Interval (CI) for the difference will also be presented. For **Secondary and exploratory endpoints** the following calculations and comparisons will be performed: - Pre- and post- baseline ARR (1 year) will be compared by ANOVA or Wilcoxon signed-rank test if data is not normally distributed. The 95% Confidence Interval (CI) for the difference will also be presented. - For all other secondary endpoints, 95% CI will be calculated for the result at each timepoint and for the differences whenever applicable, using appropriate methods. C CI
Milestones	First Patient Signed ICF: Q4 2019 Last Patient Signed ICF: Q3 2022 Last Patient Last Visit (LPLV): Q3 2024 Clinical Study Report: Q2 2025

5 Amendments and Updates

Protocol amendment 1: version 1.1 dated 31 March 2020

- Administrative changes including updated SmPC language and Merck name

Protocol amendment 2: version 2.0 dated 7 April 2021

- Reduction of the sample size
- Addition of two interim analyses
- Remote PRO completion allowed when remote consent is authorized
- Extension of the recruitment period
- Administrative changes including updated wording to Eligibility Criteria #4 for clarity

6 Milestones

Milestone	Planned date
Start of data collection	Q4 2019
End of data collection	Q3 2024
Final report of study results	Q2 2025

7 Rationale and Background

7.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic autoimmune, inflammatory neurological disease of the central nervous system (CNS) (Calabresi 2004, Hauser 2008). MS attacks the myelinated axons in the CNS, destroying the myelin and the axons to varying degrees (Weinshenker 1996, Olek 2011).

The course of MS is highly varied and unpredictable. In most patients, the disease is characterized initially by episodes of reversible neurological deficits, which are often followed by progressive neurological deterioration over time.

In Europe there are more than 600,000 patients estimated to be suffering from MS, with a median prevalence of 100 cases and a median incidence of 5.5 cases per 100,000 (Bezzini, 2017), and 50% of patients will need help walking within 20 years after the onset of the disease (Brown 2019).

Twice as many women are affected as men, and persons of Northern European descent appear to be at highest risk for MS (Hauser 2008, Cree 2007). The disease is diagnosed on the basis of clinical findings and supporting evidence from ancillary tests, such as magnetic resonance imaging (MRI) of the brain and examination of the cerebrospinal fluid (CSF). MS typically presents in adults 20 to 45 years of age; occasionally, it presents in childhood or late middle age (Cree 2007).

The cause of MS is unknown, but it appears to involve a combination of genetic susceptibility and a nongenetic trigger, such as a virus, metabolism, or environmental factors resulting in a self-sustaining autoimmune disorder that leads to recurrent immune attacks on the CNS (Cree 2007).

Neurologists agree that patients may be grouped into four major categories based on the course of disease (Hauser 2008, Goldenberg 2012):

1. *Relapsing–remitting MS:* the most common form, affecting about 85% of MS patients. It is marked by flare-ups (relapses or exacerbations) of symptoms followed by periods of remission, when symptoms improve or disappear.
2. *Secondary progressive MS:* may develops in approximately 50% of patients with relapsing-remitting disease within 20 years of disease progression (Brown 2019). For many patients, treatment with disease-modifying agents helps delay such progression. The disease course continues to worsen with or without periods of remission or leveling off of symptom severity (plateaus).
3. *Primary progressive MS:* affects approximately 10% of MS patients. Symptoms continue to worsen gradually from the beginning. There are no relapses or remissions, but there may be occasional plateaus. This form of MS is more resistant to the drugs typically used to treat the disease. Currently only ocrelizumab has been approved for the treatment of PPMS.
4. *Progressive-relapsing MS:* a rare form, affecting fewer than 5% of patients. It is progressive from the start, with intermittent flare-ups of worsening symptoms along the way. There are no periods of remission.

7.2 MAVENCLAD ® (Cladribine Tablets) 3.5 mg/kg

Recently, the number of available disease-modifying therapies for treatment of relapsing-remitting MS (RRMS) has increased (Carrithers 2014, Wingerchuk 2014). However, many patients treated with these agents continue to experience relapses and disease progression (Tsivgoulis 2015, Hadjigeorgiou 2013, Tramacere 2015); thus, new treatment options are still required. Cladribine, a synthetic deoxyadenosine analog that acts in peripheral tissues, enters the CNS and is taken up by lymphocytes and phosphorylated by deoxycytidine kinase, resulting in targeted and sustained reductions of the T and B lymphocytes that are implicated in the pathogenesis of MS (Leist 2011).

In the Phase III CLARITY study treatment with Cladribine tablets given in short courses annually for 2 years significantly improved clinical and MRI outcomes (Giovannoni 2010). Lymphopenia was the most commonly reported adverse event (AE) (Cook 2011). In CLARITY Extension, the clinical benefits of 2 years of treatment with Cladribine tablets were shown to be durable, without further active treatment (Giovannoni 2017). In the ORACLE-MS study, Cladribine tablets significantly reduced the risk of clinically definite MS in patients with a first clinical demyelinating event compared with placebo (Leist 2014), while in the ONWARD study it further reduced the ARR when co-administered with IFN- ß (Montalban 2018).

7.3 Expected contribution of this study to the knowledge on Cladribine tablets in RRMS

The main aim is to study in the real world setting the effectiveness of Cladribine tablets in terms of ARR and disability progression, in patients that switch from a first line drug (Interferons, Glatiramer Acetate, Teriflunomide, DMF).

In the CLARITY study approximately. 30% of participants were pre-treated with Interferons or Glatiramer Acetate. On the other hand, the ONWARD study has shown a significant reduction in ARR when comparing the pre-baseline treatment period with the Cladribine tablets treatment period. However, the study allowed all IFNs as pre-baseline treatments and pooled them together in the analysis. It was also not powered to detect differences in ARR and it did not include other first line treatments (DMF and Teriflunomide) in the analysis.

Here we want to evaluate the reduction in ARR afforded by Cladribine tablets, compared to the pre-baseline period, in patients treated with all first line drugs, who switch to Cladribine tablets according to the decision of their treating physician.

8 Research Question and Objectives

The main aim is to study in the real world setting the effectiveness of Cladribine tablets in terms of ARR and disability progression, in patients who switch from a first line drug (Interferons, Glatiramer Acetate, Teriflunomide, DMF).

8.1 Primary Objective

- To study the change in annualized relapse rate (ARR) in patients switching from first-line DMDs to Cladribine tablets, between the 12-month pre-baseline period and over the 12 months period before End of Study follow-up (2 years)

8.2 Secondary Objectives

- To assess change in annualized relapse rate (ARR) in patients switching from first-line DMDs to Cladribine tablets, between the 12-month pre-baseline period and over the 12 months period after initiation of Cladribine tablets (1 year)
- To assess disability progression. Disability progression is defined as progression on ⩾1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ⩾24 weeks apart and with a ⩾20% minimum threshold change for T25FW and 9HPT. T25FW and 9HPT are optional and will be performed if done as per routine practice. Progression on EDSS is defined as at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score is 0.
- To assess disability improvement. Disability Improvement is defined as improvement on ⩾1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ⩾24 weeks apart and with a ⩾20% minimum threshold change for T25FW and 9HPT. T25FW and 9HPT are optional and will be performed if done as per routine practice. Improvement on EDSS is defined as a decrease in EDSS by at least 1 point (1.5 points if baseline EDSS was 1.5).
- To assess safety of Cladribine tablets in the real world, at two years
- To assess Quality of Life and treatment satisfaction
- To assess treatment adherence
- CCI [redacted]

Exploratory Objectives

- For those patients that the treating physicians decide to prescribe an MRI at baseline and/or Year 2:
  1. To compare MRI characteristics between baseline and Years 1 and 2
  2. To compare MRI characteristics between the 12-month pre-baseline and post-baseline results (Years 1 and 2)
- To study effectiveness in 5 subgroups, defined according to the pre-baseline DMD treatment (IFN- ß 1a / IFN- ß 1 ß / Glatiramer Acetate, Teriflunomide, DMF).

9 Research Methods

9.1 Study Design

9.1.1 Design Overview

This is a prospective, non-interventional, multicenter, Phase IV study in patients with a confirmed diagnosis of RRMS who switched from first-line DMD treatment (Interferons, Glatiramer Acetate, Teriflunomide, DMF) to treatment with Cladribine tablets in routine clinical practice.

No study specific interventions will be performed on the patients and there will not be any study specified visits. Assessments planned in this protocol will be according to clinical practice.

Patients will be enrolled consecutively at study sites in the participating countries. Each patient will be followed for the course of their standard Cladribine treatment (approximately 2 years according to clinical practice).

Figure 1 provides a schematic overview of the study design. Figure 2 provides an overview of the patient journey within the study. Enrolment may take place from the time of cladribine prescription up until the second treatment week, in the first treatment year.

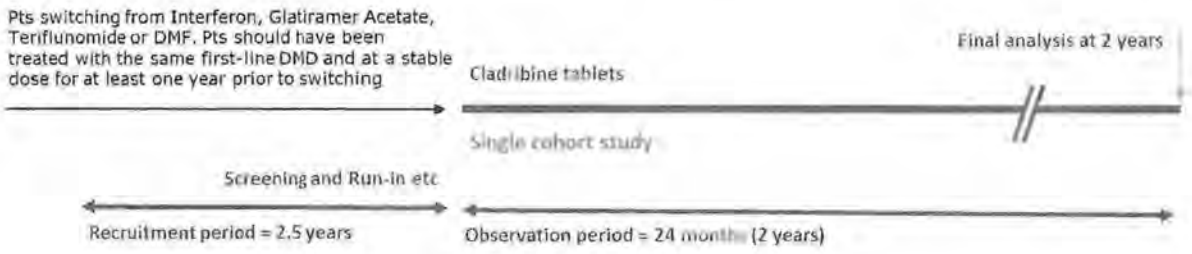

Figure 1 – Schematic of Study Design[3]

[3] Pts: patients; IFN: Interferon; DMF: Dymethyl fumarate; DMD: Disease Modifying Drug

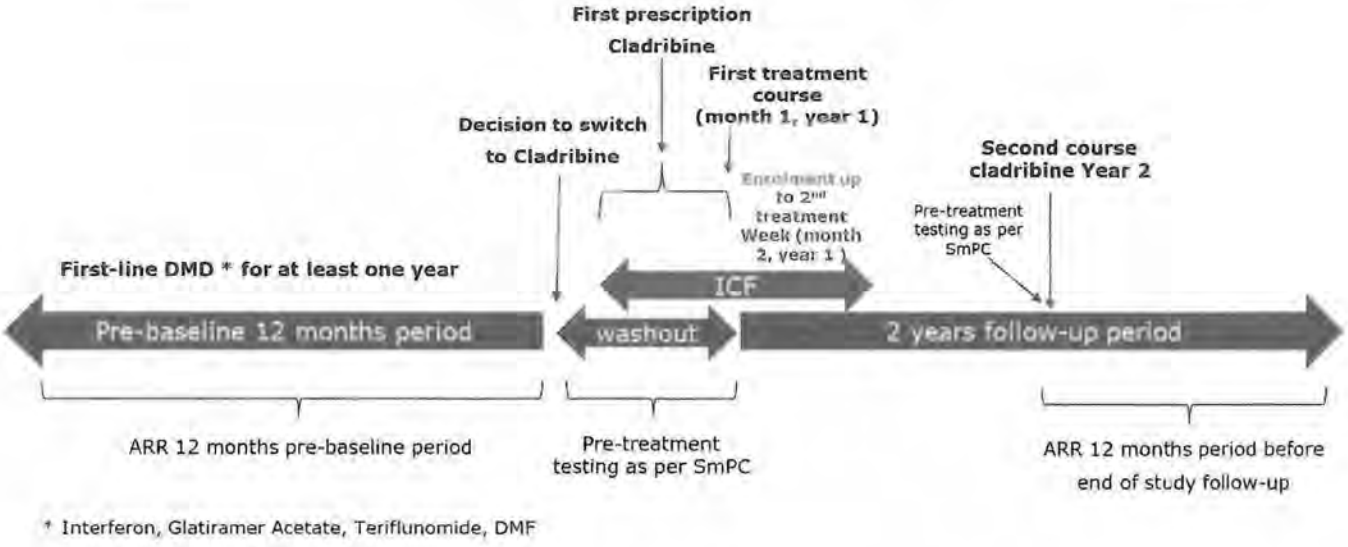

Figure 2 – Study Patient Journey

9.1.2 Outcomes

9.1.2.1 Primary

Difference in ARR between the pre-baseline 12-month period over the 12 months period before the End of Study follow-up (2 years)[4].

9.1.2.2 Secondary

- Difference in ARR between the pre-baseline 12-month period and over the 12 months period after the start of cladribine (1 year)
- Percentage of patients with 6-month disability progression[5] at the end of the study follow-up period (2 years), measured as EDSS, T25FW (optional) and 9-HPT (optional).

[4] Relapses will be diagnosed by the treating physicians, as per routine clinical practice; a typical definition within this context is the appearance of new symptoms of the exacerbation of pre-existing symptoms that are attributed to MS and occur over a minimum of 24 hours and separated from a previous attack by at least 30 days, in the absence of fever or infection.

[5] Disability progression is defined as progression on ≥1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ≥24 weeks apart and with a ≥20% minimum threshold change for T25FW and 9HPT. Progression on EDSS is defined

- Percentage of patients with 6-month disability improvement[4] at the end of the study follow-up period (2 years), measured as EDSS, T25FW (optional) and 9-HPT (optional)
- Occurrence of adverse events and of serious adverse events
- Quality of life (MSIS-29)
- Treatment Satisfaction (TSQM v1.4)
- CCI [redacted]
- Treatment adherence, assessed as percentage of cladribine tablets taken versus prescribed dose

9.1.2.3 Exploratory

- Number of MRI lesions (T2, T1 Gd+, CUA) at baseline and years 1 and 2
- Comparison of the number of MRI lesions (T2, T1 Gd+, CUA) between the pre-baseline 12 months and post-baseline results (years 1 and 2)
- An exploratory subgroup analysis will be conducted on effectiveness endpoints, with 5 groups defined according to the pre-baseline DMD treatment (IFN- ß 1a / IFN- ß 1 ß / Glatiramer Acetate, Teriflunomide, DMF)

9.2 Setting

9.2.1 Study Population

The study population will be identified according to the below inclusion and exclusion criteria. For inclusion in the study, all of the following inclusion criteria must be fulfilled:

1. Patients must voluntarily give written informed consent. Patients must read and fully understand the Informed Consent Form (ICF)
2. Adult patients, males or females patients ≥ 18 years old.
3. Patients with confirmed diagnosis of Relapsing-Remitting Multiple Sclerosis (RRMS) diagnosed by the treating physician according to applicable clinical practice guidelines – (currently McDonald 2017 criteria), with high disease activity.

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as at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score is 0. Disability Improvement is defined as improvement on ⩾1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ⩾24 weeks apart and with a ⩾20% minimum threshold change for T25FW and 9HPT. Improvement on EDSS is defined as a decrease in EDSS by at least 1 point (1.5 points if baseline EDSS was 1.5). T25FW and 9HPT are optional and will be performed if done as per routine practice.

4. Patients should have been treated with the same first-line DMD (Interferons, Glatiramer Acetate, Teriflunomide, DMF) and at a stable dose for at least one year prior to switch to Cladribine tablets and should have been prescribed Cladribine tablets, according to the decision of the treating physician, prior to enrollment in the study. Any washout period and/or washout methods required before switching (such as elimination of Teriflunomide) must have been conducted, according to the decision of the treating physician.
5. Required history data should be available:
   - MS data for the 12-months pre-baseline period (annualized relapse rate)
   - MS Medication History (prior DMDs)
6. Fulfilment of the criteria for treatment with Cladribine tablets per standard of care in accordance with the local SmPC

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

1. Contraindications to use of cladribine tablets according to the Summary of Product Characteristics
2. Patients with history of alcohol or drug abuse that could potentially interfere with their participation in the study.
3. Patient that have received Cladribine in the past
4. Concurrent participation in an investigational study in which patient assessment and/or treatment may be dictated by a protocol.

9.2.2 Definition of Study Cohorts and Description of Treatments

This is a single cohort study enrolling all patients that switch to Cladribine tablets from first-line DMDs, according to the decision of the treating physician. Patients should have been under treatment with first-line DMDs for at least one year prior to switching (see Section 9.2.1) and should have been prescribed to Cladribine tablets prior to enrollment (baseline visit). Enrollment may take place from the time of cladribine prescription up until the second treatment week, in the first treatment year.

All eligible patients are treated with Cladribine tablets in routine clinical practice. Patients will receive Cladribine as per the SmPC and the discretion of their treating physician. According to the SmPC, 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 treatment year. Each treatment week consists of 4 or 5 days on which a patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. If necessary, the treatment course in Year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes (at least 800 cells/mm³). If this recovery takes more than 6 months, the patient should not receive Cladribine tablets anymore. In patients where cladribine tablet treatment was delayed, follow-up will remain 2 years after enrollment and will not be extended by the period by which treatment was delayed.

9.2.3 Observation Period

Each patient will be followed from the date the Informed Consent is signed until they are lost to follow-up, withdrawal of consent, death or the end of the data collection period, whichever comes first. Patients will be followed for 24 months from first dose of Cladribine. Follow-up will continue regardless of cladribine tablets discontinuation for 2 years after first dose or until withdrawal.

9.2.4 Frequency of Assessments

An overview of the study with a summary of planned assessments is provided in Table 1.

Table 1 – Schedule of Assessments

Assessments	V 0 (baseline)	V 1	V 2	V 3	V 4
Indicative month	0	6	12	18	24
Informed Consent	X				
Inclusion/exclusion criteria	X				
Demographics	X				
Weight	X		X		
Relevant medical history	X				
Concomitant treatments	X	X	X	X	X
MS medication history	X				
MS Data history (within 12 months prior to switching)[a]	X				
Therapy with Cladribine tablets	X	X	X	X	
Reason for switching from first line DMD to Cladribine tablets	X				
Disability (EDSS)	X	X	X	X	X
Disability (9HPT) - optional	X	X	X	X	X
Disability (T25FW) - optional	X	X	X	X	X
Relapse count	X	X	X	X	X
Evaluation of MRI (if available)	X	X	X	X	X
CCI [redacted]	X		X		X
Collection of treatment satisfaction (TSQM-1.4)		X	X	X	X
Safety recording and reporting	X	X	X	X	X

a MS related data comprise:

- MS Medication History: Disease modifying drug (DMD)
- MS History, including number of relapses within 12 months before initiation of Cladribine therapy and number of new/enlarged MRI lesions (T1 Gd+, T2 and CUA lesions) measured on the last MRI performed per clinical practice before initiation of Cladribine therapy compared to 12-month pre-baseline MRI

As this is a non-interventional study, study assessments are part of the routine practice and related data will be collected during the visits in line with the SmPC and as clinically indicated. Patients will attend the sites as per routine practice at the discretion of the treating physician. Therefore, the timing of the visits is an approximation.

The first visit will be the baseline visit. Patients who meet all eligibility criteria and who sign the ICF can be enrolled into the study. Inclusion can occur at the time point of treatment prescription with Cladribine tablets up until the second treatment week of the first treatment year. Baseline data will be collected at the time of the visit.

In addition to the baseline data, data collection is planned at 4 supplementary visits **according to routine practice:** at month 6, 12, 18 and 24 approximately.

Baseline assessments (V0)

- Demography: Gender, age, race (if allowed per local regulation)
- Weight
- Relevant Medical History: Malignancies (as mandated in the SmPC), severe and opportunistic infections
- MS Medication History: Disease modifying drug (DMD), immunosuppressive/immunomodulatory agents (other than DMD, such as corticosteroid treatment)
- Concomitant treatments
- Reason for switching from first line DMD to Cladribine tablets (clinical relapses or disability progression, new or enhancing MRI lesions, or other).
- Date of start of therapy with Cladribine tablets and number of tablets taken
- Participation in a Cladribine Patient Support Program
- MS data History, including number of relapses within 12 months before initiation of Cladribine therapy and number of new/enlarged MRI lesions (T1 Gd+, T2 and CUA lesions) measured on the last MRI performed per clinical practice within the last 12 months before initiation of Cladribine therapy
- MSIS-29 Questionnaire: to be answered by the subject
- EQ-5D-3L Questionnaire: to be answered by the subject
- EDSS, T25FW, 9-HPT, T25FW and 9HPT are optional and will be performed if done as per routine practice.
- Safety recording and reporting
- Upon availability: MRI (T1 Gd+, T2 and CUA lesions). These assessments are not mandatory parts of this study; however, we kindly ask for providing the scores in case the tests were carried out due to medical reasons or as part of the clinical routine.

Visit 1 assessments (V1, indicative Month 6)

- Total number of relapses while in study, up until this visit
- Date of administration of therapy with Cladribine tablets and number of tablets taken versus prescribed dose
- Concomitant treatments
- TSQM-v1.4 Questionnaire: to be answered by the subject
- EDSS, T25FW, 9-HPT, T25FW and 9HPT are optional and will be performed if done as per routine practice
- Safety recording and reporting
- Upon availability: MRI (total number of T1 Gd+, T2 and CUA lesions). These assessments are not mandatory parts of this study; however, we kindly ask for providing the scores in case the tests were carried out due to medical reasons or as part of the clinical routine.

Visit 2 assessments (V2, indicative Month 12)

- Weight
- Concomitant treatments
- Total number of relapses while in study, up until this visit
- Date of administration of therapy with Cladribine tablets and number of tablets taken versus prescribed dose
- TSQM-v1.4 Questionnaire: to be answered by the subject
- MSIS-29 Questionnaire: to be answered by the subject
- EQ-5D-3L Questionnaire: to be answered by the subject
- EDSS, T25FW, 9-HPT, T25FW and 9HPT are optional and will be performed if done as per routine practice.
- Safety recording and reporting
- Upon availability: and MRI (total number of T1 Gd+, T2 and CUA lesions). These assessments are not mandatory parts of this study however we kindly ask for providing the scores in case the tests were carried out due to medical reasons or as part of the clinical routine.

Visit 3 assessments (V3, indicative Month 18)

- Total number of relapses while in study, up until this visit
- Date of administration of therapy with Cladribine tablets and number of tablets taken versus prescribed dose
- Concomitant treatments
- TSQM-v1.4 Questionnaire: to be answered by the subject

- EDSS, T25FW, 9-HPT, T25FW and 9HPT are optional and will be performed if done as per routine practice
- Safety recording and reporting
- CCI [redacted]

Visit 4 assessments (V4, indicative Month 24)

- Total number of relapses while in study, up until this visit
- Concomitant treatments
- TSQM-v1.4 Questionnaire: to be answered by the subject
- MSIS-29 Questionnaire: to be answered by the subject
- EQ-5D-3L Questionnaire: to be answered by the subject
- EDSS, T25FW, 9-HPT, T25FW and 9HPT are optional and will be performed if done as per routine practice.
- Safety recording and reporting
- CCI [redacted]

A patient is considered to have completed the study after they have had a follow-up visit at the end of the observation period of 24 months. Study termination earlier than month 24 may occur due to lost to follow up, informed consent withdrawal or any other reasons as recorded. Following assessments will be performed at study termination, if this information is available:

- Weight
- Total number of relapses while in study
- TSQM-v1.4 Questionnaire: to be answered by the subject
- MSIS-29 Questionnaire: to be answered by the subject
- CCI [redacted]
- EDSS, T25FW, 9-HPT, T25FW and 9HPT are optional and will be performed if done as per routine practice.
- Safety recording and reporting
- Upon availability: MRI (total number of T1 Gd+, T2 and CUA lesions). These assessments are not mandatory parts of this study however we kindly ask for providing the scores in case the tests were carried out due to medical reasons or as part of the clinical routine.

For patients lost to follow up observations will be censored and will be handled as defined in the SAP. Lost-to follow-up is confirmed when at least 3 documented attempts to reach out the

patient have been made. If a subject is lost to follow-up, every possible effort must be made by study center personnel to contact the subject and determine the reason for discontinuation. The measures taken to follow-up must be documented. If a subject discontinues before completion of study procedures, the reason for discontinuation must be documented in the case report form (CRF) and source documents.

Safety data assessment

- Safety events are collected throughout the study as described in Section 11.5.

9.2.5 Withdrawal from the Study

Patients may discontinue from the study at any time (withdraw consent). The reason for any study discontinuations will be collected, if available.

Patients who discontinue treatment will continue to be followed until end of follow-up period regardless of treatment status, unless they switch to another DMD treatment in which case they should be withdrawn from the study.

9.3 Variables

- Demographic data: Gender, age, race (if allowed as per local regulation)
- Other Baseline Assessments: Weight
- Medical history, including MS, malignancies, severe and opportunistic infections
- MS-Medication history: DMD, immunosuppressive/immunomodulatory agents (other than DMD, such as corticosteroid treatment)
- Therapy with Cladribine Tablets [date of administration and number of tablets taken versus prescribed dose (treatment adherence)]
- Reason for switching from first line DMD to Cladribine Tablets
- Participation in a Cladribine Patient Support Program
- Course of disease
    - Relapses
    - MRI data
        - T2, T1 Gd+ and CUA lesion counts
    - EDSS Score
    - T25FW (time in seconds, optional)
    - 9-HPT (time in seconds, optional)
- TSQM-v1.4 VAS score
- MSIS-29 score

- EQ-5D-3L score
- Safety (Serious Adverse Events (SAEs), Adverse Events of Special Interest (AESI) and Adverse Drug Reactions (ADRs))

Derived and transformed data needed for the analysis are described in Section 9.7.2.

9.4 Data Source

The data to be collected in the study will be obtained by means of an (e)CRF. The data in the (e)CRF should be consistent with the relevant source documents. Further details are provided in Section 9.6.

Patients will complete the MSIS-29, EQ-5D-3L and TSQM v1.4 questionnaires at the sites and the information will be transcribed into the eCRF by the investigator site staff. Patients can complete the MSIS-29 and EQ-5D-3L remotely at baseline when remote consent is performed and authorized in the country.

Pre-baseline data, listed in Section 9.2.4, will be obtained from patient records and will be transcribed into the eCRF by the investigator site staff.

9.5 Study Size

242 patients with confirmed diagnosis of Highly Active Relapsing-Remitting Multiple Sclerosis (RRMS) will be enrolled in the participating countries.

CCI [redacted]

9.6 Data Management

The main purpose of the (e)CRF is to obtain data required by the non-interventional study protocol in a complete, accurate, legible and timely manner. The data in the (e)CRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this study is accurate and documented appropriately on all applicable forms. Data will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the (e)CRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

The data will be entered into a validated database. The Sponsor/CRO or its designee will be responsible for data processing, in accordance with the Sponsor's/CRO's data management procedures. Database lock will occur once quality control and quality assurance procedures (including SAE/SADR reconciliation) and coding activities have been completed. PDF files of the (e)CRFs will be provided to the investigators at the completion of the study.

9.7 Data Analysis

Statistical programming and analyses will be performed using SAS 9.4 (or higher). Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP), which will be finalized prior to database lock and will be included in the clinical study report for this protocol. The final SAP will take into account any amendment to the protocol.

All analyses will be performed on patients who received at least one dose of Cladribine tablets following enrollment in the study.

9.7.1 Analysis Sets

Full Analysis Set

The Full Analysis Set (FAS) is defined as all the patients who provided informed consent and who received at least one dose of Cladribine. A subgroup analysis will be conducted on FAS, as described in Section 9.7.3.

9.7.2 Derived and Transformed Data

Missing information will be captured for quantitative as well as qualitative variables by the category "Missing" in the summary statistics. If there are no missing values this will be indicated by "0" unless otherwise specified. Due to the longitutinal nature of the data and the lengthy follow-up period, it is possible that missing outcome data will be present. Patterns and degrees of missingness will be summarized. In general no imputation of missing data will be done.

9.7.3 Statistical Methods

All endpoints will be presented by descriptive statistics for baseline, 12-months, and End of Study assessments. Assessments done at 6-months and 18-months will be presented similarly. Quantitative (continuous) variables will be summarized with the use of descriptive statistical measures [mean value, standard deviation (SD), median, min-max, Q1-Q3]. Qualitative (categorical) variables will be displayed as frequencies and percentages (N, %).

The normality of distributions will be examined using the Shapiro-Wilk test in order to determine whether or not to use parametric methods for analysis.

Primary Endpoint: Pre- and post- baseline ARR will be compared by ANOVA or Wilcoxon signed-rank test if data is not normally distributed. The 95% Confidence Interval (CI) for the difference will be presented.

If appropriate, sensitivity analyses will be done to determine the impact of confounding factors or to describe the outcome for special subject groups fulfilling predefined criteria. Details will be described in the SAP.

For **Secondary and exploratory endpoints** the following calculations and comparisons will be performed:

- Pre- and post- baseline ARR (1 year) will be compared by ANOVA or Wilcoxon signed-rank test if data is not normally distributed. The 95% Confidence Interval (CI) for the difference will be presented.
- For all other secondary endpoints, 95% CI will be calculated for the result at each timepoint and for the differences whenever applicable, using appropriate methods.

In the analysis of 6-month disability progression/improvement EDSS, T25FW and 9-HPT values must be obtained at sequential time points, separated by 6-month intervals. As T25FW and 9-HPT are optional and will be performed if done as per routine practice, missing values may occur and could lead to bias in their analysis. Methods to handle this bias issue will be described in detail in SAP.

A subgroup analysis will be conducted on effectiveness endpoints (ARR at 1 and 2 years, percentage of patients with 6-month disability progression and improvement), with 5 groups defined according to the pre-baseline DMD treatment (IFN- ß 1a / IFN- ß 1 ß / Glatiramer Acetate, Teriflunomide, DMF).

CCI [redacted]

9.7.4 Sequence of Analyses

Main analysis will be performed once all the patients completed the study with the purpose of evaluating all endpoints and database is locked. Two descriptive interim analyses will be performed, respectively when 30% and 60% of the patients have completed the 12-month follow-up visit, to also observe pre-baseline ARR and the variances adherence with sample size assumptions. An alpha adjustment for the multiplicity of the analysis will be introduced if the interim analysis will lead to change in sample size strategy . The Interim Analyses will be based on a subset of main analysis outputs and the list will be detailed in the SAP.

9.8 Quality Control

Quality control activities will include verification of data and ensure the data collected in (e)CRF is accurate, valid and in accordance with the protocol.

9.9 Limitations of the Research Methods

This study is open label and observational, and therefore has inherent limitations in terms of susceptibility to bias, confounding and restricting the ability to define causality. There is limited control over patient assessment as patient monitoring and diagnostics are per standard of care; no additional clinical monitoring is generally conducted. Patient specific methodological challenges such as potential biases from patient selection, loss of patients through study attrition, and overall patient recall are also other limitations. However, observational study strengths include that they reflect daily clinical practice more closely than randomized controlled trials, both in terms of the heterogeneous patient populations that are included, and the medical interventions that they receive. Real-life observational data is essential to assess and improve clinical practice worldwide and complement randomized controlled trials by providing clinically-relevant, real-world data and provide considerable health economic information.

9.10 Other Aspects

9.10.1 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the study at a given site, the protocol will be submitted together with its associated documents (informed consent form, PROs, etc,) to the responsible Independent Ethics Committee (IEC) for its favorable opinion/approval. The written favorable opinion/approval of the IEC will be filed by the Investigator and a copy will be sent to the Sponsor.

The study must not start at a site before the Sponsor has obtained written confirmation of favorable opinion/approval from the concerned IEC. The IEC will be asked to provide documentation of the date of the meeting at which the favorable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favorable opinion/approval that clearly identifies the study, the protocol version, and the Subject Information and Consent Form version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to the protocol will also be submitted to the concerned IEC, before implementation in case of substantial changes.

9.10.2 Monitoring

Risk based monitoring will be performed for this study. Risk based monitoring is the process of ensuring the quality of clinical studies by identifying, assessing, monitoring and mitigating the risks that could affect the quality or safety of a study. It can facilitate efficient trial delivery without compromising patient safety or data quality. A Sponsor or an appointed CRO will identify critical data and processes, performs a risk assessment and then develops a monitoring plan that focuses on the important and likely risks to critical data and processes.

A Sponsor or an appointed CRO Monitor will mainly perform 'remote' monitoring calls at regular intervals.

'On site' visits may be performed, if required, at any time during the study. For hospitals where potential quality risks are identified, on-site visits can verify that the study is being carried out according to the protocol.

Monitoring on-site visits will involve checking of CRFs against original patient records and identification of any questions or problems related to study conduct or data collection. Investigators must therefore ensure that the Monitor has access to relevant documents during monitoring visits, and that they and/or relevant site staff members are available to discuss any issues that may arise.

The study Monitor will send monitoring reports to the Sponsor.

9.10.3 Health Authorities

The protocol will be notified to the National Health Authorities register in accordance with the regulations of each country for non-interventional studies.

9.10.4 Quality Assurance

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IECs may conduct quality assurance audits/inspections at any time during or following a study. The Investigator must agree to allow auditors/inspectors direct access to all study-related documents, including source documents, and must 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.

The protocol, each step of the data capture procedure, and the handling of the data, as well as the study report, may be subject to independent Clinical Quality Assurance. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.10.5 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 or the first publication of study results, whichever comes later. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10 Protection of Patients

10.1 Subject Information and Informed Consent

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.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his/her designee will inform the subject verbally of all pertinent aspects of the study (the language used in doing so must be chosen so that the information can be fully and readily understood by laypersons). Depending on national regulations, a person other than the Investigator may inform the subject and sign the Informed Consent Form.

The Informed Consent Form must be signed and personally dated by the subject and the Investigator. The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived by the Investigator. A copy of the signed and dated information and consent form should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to patients will be revised by the Sponsor and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be forwarded to each subject in the study. The Investigator will explain the changes to the previous version.

10.2 Subject Identification and Privacy

A unique patient number will be assigned to each subject at inclusion. This number will serve as the subject's identifier in the study as well in the study database.

The Investigator must ensure that the patients' anonymity is maintained. On the CRFs or other documents submitted to the Sponsor, patients should not be identified by their names, but by their

assigned identification numbers. If subject names are included on copies of documents submitted to the Sponsor, the names (except for initials) must be obliterated and the assigned subject numbers added to the documents.

The Investigator should keep a separate log of patients' identification numbers, names, addresses, telephone numbers and hospital numbers (if applicable). Documents not for submission to the Sponsor, such as signed Informed Consent Forms, should be maintained in strict confidence by the Investigator.

Only authorized persons will have access to identifiable personal details, if required for data verification. The subject's original medical data that are reviewed at the site during source data verification by the Monitor, audits, and Health Authority inspections will be kept strictly confidential. The Investigator agrees to provide direct access to these documents to the Sponsor and to Health Authority representatives. The Investigator is responsible for retrieving information from personal medical records.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Patients will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

11 Management and Reporting of Adverse Events

11.1 Adverse Events

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 Drug Reaction (ADR)

An ADR 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.

ADRs 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 off-label use, overdose, misuse, abuse and medication errors.

Reports of Special Situations: Pregnancy, overdose, off-label use, misuse, medication error or occupational exposure, lack of therapeutic effectiveness and others

- 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, e.g. 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 submitted to the authorities as ICSRs. They will be collected and considered in the study report or any interim reports, as applicable.

Serious Adverse Event (SAE)/Serious Adverse Drug Reaction (SADR)

An SAE/SADR is any AE/ADR 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 as serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardise the patient or might require an intervention to prevent one of the other outcomes listed above. Such important medical events should be considered as serious.

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 hospitalization or development of dependency or abuse. As a guidance, the important medical event (IME) terms list is intended to be used for assessment of suspected adverse reactions (see EMA/207865/2017).

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

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. AESIs for monitoring should then be collected following the procedure for an SAE described in Section 11.4.

The study-specific data will be registered for each of the following events and the known related risk factors:

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.

Malignancy: Any occurrence of malignant neoplasms during the study period. These will be classified overall and by type. Malignancies will include all physician-diagnosed and pathologically confirmed solid tumours (including non-melanoma skin cancer) and lymphoproliferative/ haematopoietic neoplastic diseases. Benign tumours will not be collected.

Severe and/or serious infections: The above mentioned 4 categories will follow as: Any occurrence during the study period, regardless of the causative agent and the duration of infection, will be recorded. All of the following will be considered:

- Bacterial, viral, fungal, parasitic and protozoal infections
- Severe and/or serious infections will be defined by their management or their outcome: all infections that result in death or hospitalisation or require the use of intravenous treatment (e.g. antibiotics)
- Opportunistic infections are 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; opportunistic infections exclude herpetic infection
- Herpes zoster (not considered an opportunistic infection). Only severe and/or serious herpes zoster will be collected.

The duration of infections will be the difference between start date and recovery date as reported by the treating physician.

Patients may contribute more than 1 episode to this analysis if, after resolution as defined, another infection occurs.

Severe lymphopenia: Any occurrence of severe (or worse) 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 (severe lymphopenia): <500 - 200/mm^3; <0.5 - 0.2 x10^9 /L
- Grade 4 (serious lymphopenia): <200/mm^3; <0.2 x 10^9 /L

Duration of severe lymphopenia: It is defined as the interval from the finding of severe lymphopenia until resolution, which is the achievement of a CTCAE Grade 1 [ranging from the

lower limit of normal (LLN) to 800/mm^3] or normalization (above LLN i.e. normal lymphocyte count or CTCAE Grade 0). Patients may contribute more than 1 episode to this analysis if, after resolution as defined, severe lymphopenia occurs again. 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 Cladribine tablets dosing and during episodes of severe lymphopenia.

Events not to be considered as Adverse Events
Medical conditions present at study start, that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are NOT to be considered AEs.

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 any study medication.

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

The recording period for AEs begins, when the subject is initially included in the study (date of signature of first informed consent) and continues at least end of the mandatory safety-follow-up period at last study visit. However, as enrollment may take place from the time of cladribine prescription up until the second treatment week, in the first treatment year, any ADRs assessed as related to cladribine by the Investigator after the first dose of cladribine but before signature of Informed Consent must be recorded in the eCRF as well.

All adverse events, as specified above, occurring during the study, must be documented by the Investigator in the eCRF, including its description, seriousness, severity (grading), duration (onset

and resolution dates), causal relationship, any other potential causal factors, actions taken with the study drug (e.g. dose reduction, withdrawal), required treatment and outcome of the AE.

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

Death, disability, and hospitalization are considered outcomes in the context of safety reporting and not usually considered ARs/AEs. Therefore the primary cause of death, disability or hospitalization should be recorded and reported as an SAE/AR, and the outcome should be recorded in a separate data field. However, 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 an SAE. "Fatal" will be recorded as the OUTCOME of this respective event and not be as separate event. Only, if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might then be reported as an SAE.

Reports of Special Situations (see definition) are also to be recorded in the CRF following the AE procedure, even if occurring without AE.

Pregnancy and Breastfeeding. Pregnancy or breastfeeding must be recorded in the CRF 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.

Women who become pregnant under therapy with Cladribine tablets should discontinue treatment.

11.5 Safety Data Collection for Reporting

Safety data collection forms:

The following safety data collection forms are used in this study:

- (Serious) Adverse Event Report Form
- Pregnancy Report Form (paper form)
- Parent-Child/Foetus AE Report Form (paper form)
- Adverse Event of Special Interest (AESI) Report Form

Reportable events:

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

- All SAEs (related or unrelated) are to be reported independent of their relationship to the study drug via the eCRF or using back-up paper forms in case of eCRF outage
- AEs of special interest (AESI) are to be reported via the eCRF or using back-up paper forms in case of eCRF outage

- Pregnancy or lactation is to be reported by using the paper 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 paper Parent-Child/Foetus Report Form

Special situations (see definition) should be reported by using the paper (Serious) Adverse Event Report Form by indicating whether serious or not

Non-serious ADRs are to be reported within 4 calendar days via the eCRF or using the paper (Serious) Adverse Event Report Form in case of eCRF outage.

Procedure for Safety Data Reporting (completion and forwarding):

For any new events that are listed in the section above "Reportable events", the Investigator/HCP will report the event by transmitting the Safety Data Collection Form in English via the eCRF or via paper (as described in the section above) to the Sponsor via CRO Safety Check Desk. The Investigator must respond to any request by CRO for follow-up information, as noted above for initial report. CRO should forward the follow-up information within 24 hours to Global Patient Safety, as noted above for initial reports. The sponsor has to meet strict regulatory timelines associated with expedited safety reporting obligations.

PPD

PPD

The data entered on the safety data collection forms must be consistent with the information recorded in the eCRF. 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 (e.g., ID number, gender, age)
- Product (including lot/ batch number)
- Description of SAE/ADR/ fatal case/ Special situation

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

When AE information is communicated via telephone, a written/EDC 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 CRF. 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.

Procedure for Follow-up Information

The Investigator must promptly respond to any request by CRO for follow-up information or questions from the Sponsor or delegate, as noted above for initial report. Such requests will be sent to the Investigator via the CRO Safety Check Desk. SAEs/ADRs/AESIs and 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 has a fatal outcome or 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/ADRs/fatal cases and special situations and AESIs missing information such as outcome, confounders, and causality is to be provided. Additionally, follow-up information of non-serious adverse drug reactions 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 event (follow-up) will follow the procedures and timelines of the original report.

CRO should forward the follow-up information within 24 hours to Global Patient Safety, as noted above for initial reports. The sponsor has to meet strict regulatory timelines associated with expedited safety reporting obligations.

11.6 Regulatory Reporting to the Health Authorities

Expedited reporting of serious AEs and non-serious adverse drug reactions to Health Authorities is performed by the Sponsor by the Global Drug Safety department, according to applicable regulations of participating countries.

In addition, the Investigator will comply with any applicable local pharmacovigilance requirements to report appropriate safety data, to national pharmacovigilance systems (e.g. Yellow Card Scheme in UK), as required by country specific reporting requirements.

12 Plans for Disseminating and Communicating Study Results

12.1 Study Report

The completed study will be summarized in a final report that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings.

12.2 Publication

The first publication will be a publication of the results of the analysis of the primary outcome(s) that will include data from all study sites.

The Investigator 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 Sponsor will not suppress or veto publications, but maintains the right to delay publication in order to protect intellectual property rights.

13 References

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14 Appendices

14.1 Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	Oral CLADribine in patients that Change from first-line Disease Modifying Treatments for Multiple Sclerosis: a pROspective effectivenesS and Safety study (CLAD CROSS)
Study Protocol Date / Version:	7 April 2021 / Version 2.0

Protocol Lead responsible for designing the non-interventional study:

I approve the design of the non-interventional study:

PPD _____ PPD _____

Signature Date of Signature

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

Signature Page – Coordinating Investigator

Study Title	Oral CLADribine in patients that Change from first-line Disease Modifying Treatments for Multiple Sclerosis: a pROspective effectivenesS and Safety study (CLAD CROSS)
Study Protocol Date / Version	7 April 2021 / Version 2.0

I approve the design of the non-interventional study and 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.

PPD

Signature Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: PPD

Address: PPD

Telephone number: PPD

E-mail address: PPD

Signature Page – Principal Investigator

Study Title	Oral CLADribine in patients that Change from first-line Disease Modifying Treatments for Multiple Sclerosis: a pROspective effectivenesS and Safety study (CLAD CROSS)
Study Protocol Date / Version	7 April 2021 / Version 2.0

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.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

E-mail address:

Sponsor Responsible Persons not Named on the Cover Page

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

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
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