Non-Interventional Study Protocol

Study Protocol Number	MS700568_0079
Title	Cladribine tablets: Observational evaluation of effectiveness and patient-reported outcomes (PROs) in subopti<u>MA</u>lly controlled patient<u>S</u> previously <u>T</u>aking oral or infusion dis<u>E</u>ase-modifying d<u>R</u>ugs (DMDs) for relapsing forms of multiple sclerosis (RMS) (MASTER-2)
Protocol Version Identifier	11.0
Protocol Date/Version	21 October 2024 / Version 11.0
Replaces Version	19 September 2024 / Version 10.0
Active Substance	Cladribine
Medicinal Product	Mavenclad®
Marketing Authorization Holder(s)	EMD Serono, Inc., Rockland, MA, USA
Research Question and Objectives	The main research questions are to evaluate the effectiveness and safety of cladribine tablets in patients with RMS, including relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (aSPMS), who transition to cladribine tablets after suboptimal response to any other oral or infusion disease-modifying drugs (DMDs) approved in the United States (US) for RMS in a real-world setting. Additionally, this study will separately describe real-world clinical and demographic characteristics among a sub-cohort of patients who transition from ocrelizumab to cladribine. Primary Objective(s): • To estimate the annualized relapse rate (ARR) over a 24-month period in patients with RMS, including RRMS and aSPMS, who are treated with cladribine tablets in a real-world setting and after suboptimal response to any other oral or infusion DMDs approved in the US for RMS

Secondary Objectives:

- To assess patient-reported outcome (PROs), treatment adherence and treatment satisfaction during treatment with cladribine tablets
- To assess treatment patterns (multiple sclerosis [MS] treatment prior to transition to cladribine tablets since MS diagnosis, concomitant treatment for MS during the last 2 years prior to transition to cladribine tablets (or since MS diagnosis, if diagnosis <24 months), follow-up treatment in case of discontinuation of cladribine tablets); and in particular, to assess the clinical and demographic characteristics related to the sequential use of ocrelizumab and cladribine
- To estimate the ARR over the 24-month period prior to initiation of cladribine tablets (or since MS diagnosis, if diagnosis <24 months)
- To collect all serious adverse events (SAEs), adverse drug reactions (ADRs), adverse events of special interest (AESIs), and special situations during and following treatment with cladribine tablets over a 24-month period

Country of Study United States

Author

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1 Table of Contents

2 List of Abbreviations

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ARR	Annualized Relapse Rate
aSPMS	Active Secondary Progressive Multiple Sclerosis
BDI-FS	Beck-Depression Inventory-Fast Screen
CBC	Complete Blood Count
CI	Confidence Interval
CNS	Central Nervous System
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CU	Combined Unique
DMD	Disease-Modifying Drug
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Score
FSS	Functional System Scores
Gd+	Gadolinium-Enhancing
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
IRB	Institutional Review Board
CCI	[redacted]
MFIS-5	Modified Fatigue Impact Scale – 5-item Version
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MS-TAQ	Multiple Sclerosis Treatment Adherence Questionnaire
PDDS	Patient Determined Disease Steps

PRO	Patient-Reported Outcome
RMS	Relapsing forms of Multiple Sclerosis
RRMS	Relapsing-remitting Multiple Sclerosis
SAE	Serious Adverse Event
SD	Standard Deviation
SF-36	36-Item Short Form Health Survey
TSQM	14-Item Treatment Satisfaction Questionnaire for Medication
US	United States
US FDA	United States Food and Drug Administration
USPI	United States Prescribing Information
WPAI-MS	Work Productivity Activity Impairment – Multiple Sclerosis
2-CdA	2-chloro-2'-deoxyadenosine

3 Responsible Parties

Responsible Parties	Contact details
Investigators	The name and contact information of all investigators will be maintained by the MAH/MAH's representative(s) in a separate document.
Operational Study Lead	PPD PPD PPD EMD Serono, Inc. A business of Merck KGaA, Darmstadt, Germany One Technology Place Rockland, MA 02370, USA PPD
Protocol Medical Lead	PPD PPD EMD Serono, Inc. A business of Merck KGaA, Darmstadt, Germany One Technology Place Rockland, MA 02370, USA PPD
Contract Research Organization	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	Cladribine tablets: Observational evaluation of effectiveness and patient-reported outcomes (PROs) in subopti<u>MA</u>lly controlled patient<u>S</u> previously <u>T</u>aking oral or infusion dis<u>E</u>ase-modifying d<u>R</u>ugs (DMDs) for relapsing forms of multiple sclerosis (RMS) (MASTER-2) Protocol Version 11.0, 21 October 2024 PPD EMD Serono, Inc. A business of Merck KGaA, Darmstadt, Germany One Technology Place Rockland, MA 02370, USA E-mail:PPD
Rationale and background	Multiple sclerosis (MS) is an immune-mediated, chronic inflammatory disease of the central nervous system (CNS) characterized by the demyelination and destruction of axons. According to a recent study by the National Multiple Sclerosis Society, there are approximately 1,000,000 persons in the United States (US) living with MS. 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. Approximately 85% of patients with MS initially have RMS which is characterized by alternating periodic acute exacerbations of disease activity (relapses) and periods of remission, consisting of partial or complete recovery. Patients with RMS are recommended to receive treatment with disease-modifying drugs (DMDs) to decrease the rate of relapse and slow the accumulation of brain lesions on magnetic resonance imaging (MRI). Numerous immunomodulatory agents with differing routes of administration (including injectable, oral and infusion) and differing mechanisms of action have been shown to have beneficial effects. Because they are not curative, most DMDs are generally continued indefinitely unless they are ineffective or not tolerated. There is currently no standard protocol to guide the choice of DMDs for patients with MS. Rather, treatment decisions and medication choices are the result of a thorough risk-benefit analysis and consideration of disease activity, patient-specific factors, and drug-related factors. Cladribine (2-chloro-2'-deoxyadenosine [2-CdA]) is a synthetic anti-neoplastic drug that belongs to the subgroup of agents called purine analogs. Cladribine tablets were indicated for the treatment of patients with RMS, including relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (aSPMS), by the US Food and Drug Administration (US FDA) in 2019. Data about the safety and effectiveness of cladribine tablets in real-world clinical settings are currently limited. Real-world data are also limited about patients' adherence to treatment with cladribine tablets, patient-reported outcomes (PROs), and treatment patterns for RMS

	before, during, and after treatment with cladribine tablets in patients with suboptimal response to prior oral or infusion DMDs.
Research question and objectives	The main research questions are to evaluate the effectiveness and safety of cladribine tablets in patients with RMS, including RRMS and aSPMS, who transition to cladribine tablets after suboptimal response to any other oral DMDs or any infusion DMDs approved in the US for RMS in a real-world setting. Additionally, this study will separately describe real-world clinical and demographic characteristics that contribute to sequential treatment patterns among a sub-cohort of patients who transition from ocrelizumab to cladribine. Primary Objective: • To estimate the annualized relapse rate (ARR) over a 24-month period in patients with RMS, including RRMS and aSPMS, who are treated with cladribine tablets in a real-world setting and after suboptimal response to any other oral DMDs or any infusion DMDs approved in the US for RMS Secondary Objectives: • To assess PROs, treatment adherence and treatment satisfaction during treatment with cladribine tablets • To assess treatment patterns (MS treatment prior to transition to cladribine tablets since MS diagnosis, concomitant treatment for MS during the last 2 years before transition to cladribine tablets (or since MS diagnosis, if diagnosis <24 months), follow-up treatment in case of discontinuation of cladribine tablets); and in particular, to assess the clinical and demographic characteristics related to the sequential use of ocrelizumab and cladribine • To estimate the ARR over the 24-month period prior to initiation of cladribine tablets (or since MS diagnosis, if diagnosis <24 months) • To collect all serious adverse events (SAEs), adverse drug reactions (ADRs), adverse events of special interest (AESIs) and special situations during and following treatment with cladribine tablets over a 24-month period
Study design	This is a prospective, observational, multicenter, 30-month, Phase IV study. Patients who had decided prior to enrollment to transition from an oral DMD or an infusion DMD to treatment with cladribine tablets under routine clinical care and who meet all eligibility criteria consistent with the approved US Prescribing Information (USPI) will receive an initial treatment course with cladribine tablets in Year 1 and are planned to receive a second course in Year 2, as per the approved USPI. Cladribine tablets are being prescribed as part of patients' standard medical care and commercial product will be used. Patients will not be provided the cladribine tablets free of charge in connection with their participation in the study. It is expected that the investigator

	considered the mode of action and duration of effect of the previous DMD prior to initiation of cladribine tablets. It is at the investigator's discretion to define this time period, following respective USPI. All treatment decisions are at the discretion of the investigator. Patients will be followed up until the end of the observation period, irrespective if they discontinue cladribine tablets during follow-up. Baseline data on previous MS DMD use, relapses during the previous 2 years (or since MS diagnosis, if diagnosis <24 months), and available baseline MRI data will be collected at the Baseline Visit. During the observation period, patients will attend visits as per routine clinical practice, which are expected to happen approximately at the end of Month 2, Month 6 and Month 12 during Year 1, and at the end of Months 14, 18, and 24 (i.e. after the second course of treatment during Year 2), as clinically indicated. In patients whose lymphocyte count has not returned to 800 cells per microliter, Year 2 treatment should be delayed as per USPI and, thus, these patients could be followed for up to 30 months. Detailed clinical data about MS disease relapses, MRI findings, hematologic and other laboratory assessments, medications received, and adverse events (AEs), as well as PROs, will be prospectively collected during the study period.
Population	Inclusion criteria: 1. Male or female patients ≥18 years 2. Signed informed consent 3. Have diagnosis of RMS, including RRMS and aSPMS, and satisfy the approved indication for cladribine tablets as per USPI 4. Have time since diagnosis of RMS of at least 12 months 5. In the opinion of the investigator, experienced suboptimal response (lack of effectiveness, intolerability, poor adherence) to oral DMD treatment other than cladribine tablets or infusion DMD treatment 6. Had received their last previous oral DMD for at least 1 month or at least 1 dose of their last previous infusion DMD 7. Have decided to initiate treatment with cladribine tablets during routine clinical care (i.e. before enrollment) 1. Meet criteria as per the approved USPI 2. Have access to a valid e-mail address Exclusion criteria: 1. Have been previously treated with cladribine in any dosing form (intravenous, subcutaneous, or oral) 2. Transitioning from previous oral or infusion DMD solely for administrative reasons such as relocation

	3. Have any clinical condition or medical history noted as contraindication on USPI 4. Are currently participating in an interventional clinical trial 5. Pregnant or breastfeeding women, women who plan to become pregnant or men whose partner plans to become pregnant during the cladribine treatment period
Outcomes	Primary Outcome: • ARR over 24 months of treatment with cladribine tablets (prospectively collected data), accompanied by 95% confidence interval (CI). For this study, a relapse will be defined as per routine clinical practice as determined by the investigator. As a guide, relapse may be defined as exacerbation of symptoms that 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. Secondary Outcomes: • Baseline scores and change in scores from baseline to Months 6, 12, and 24 for the following PROs (collected via electronic PRO [ePRO] at the practice or at the patient's home): o 14-Item Treatment Satisfaction Questionnaire for Medication (TSQM) o 36-Item Short Form Health Survey (SF-36) o Modified Fatigue Impact Scale – 5-item version (MFIS-5) o Beck-Depression Inventory – Fast Screen (BDI-FS) [7 items] o Work Productivity Activity Impairment – MS (WPAI-MS) [6 items] o Patient Determined Disease Steps (PDDS) scale. • Treatment adherence questions, based on modified versions of the Multiple Sclerosis Treatment Adherence Questionnaire (MS-TAQ); data to be collected via ePRO at baseline (modified for once or twice daily oral dosing to assess adherence during last previous oral DMD treatment or modified for infusion dosing to assess adherence to last previous infusion DMD treatment) and at the end of Months 1, 2, 13, and 14 (modified for cladribine tablets) • Proportion of patients experiencing a relapse • Proportion of patients with relapse associated with hospitalization • Proportion of patients with relapse associated with glucocorticoid use • Assessment of previous treatment for MS:

	○ Previous DMD(s) received for MS prior to study enrollment, since MS diagnosis ○ Reasons for discontinuation of previous DMD(s) • Assessment of clinical and demographic characteristics of patients who transition from ocrelizumab to oral cladribine tablets ○ Reasons for discontinuation of ocrelizumab • Proportion of patients who discontinue oral cladribine tablets ○ Reason for discontinuation of cladribine tablets ○ Elapsed time to discontinuation after first dose ○ Number of doses and % of planned doses (as per USPI) received ○ Subsequent treatment chosen following discontinuation of cladribine tablets • Assessment of concomitant MS medications used during study period • The ARR based on the last 24 months (or since MS diagnosis, if diagnosis <24 months) prior to the start of treatment with cladribine tablets (retrospective data) • All SAEs, ADRs, AESIs and special situations over a 24-month period • Absolute lymphocyte count (ALC) assessed as per USPI • Complete blood count (CBC) and lymphocyte subset information as assessed per routine clinical practice
Variables	• Baseline characteristics of patients initiating cladribine tablets: age, sex, weight, race/ethnicity, elapsed time since diagnosis of MS, elapsed time since first symptoms of MS • Medical history (including prior medications for MS) • Physical and neurological examinations • MRI results • Hematological assessments • ePRO assessments results • Relapse information
Data sources	Data sources for this study will include data extracts from patients' medical records performed by site personnel as well as questionnaires directly filled out by patients. The data to be collected in the study will be obtained by means of electronic Case Report Forms (eCRFs).

CCI [redacted]	[redacted]
Data analysis	All patients starting treatment with cladribine tablets will be included in the analyses. The primary endpoint will be analyzed at Month 24. All secondary endpoints on relapse rates, PROs, MRI, and treatment patterns will be analyzed at Month 12 (12-month interim analysis) and Month 24 (final analysis). PRO data will be analyzed once the first 30 patients reach the 6-month follow-up as well as at Month 6 for all enrolled patients. Safety data will also be assessed at Month 6 for the first 30 patients enrolled as well as at Months 12 and 24., for all patients, unless Year 2 treatment is delayed in which case the final safety assessment would occur at Month 30. Descriptive statistics will be used to summarize data. If the outcome in question is a continuous variable, the number of observations, number of missing values, mean, standard deviation (SD), median, first quartile and third quartile, minimum and maximum values will be presented; if the outcome is categorical, numbers and percentages of patients for each of the categories and numbers and percentages of missing values will be presented. Where appropriate, 95% CIs will be presented. For continuous data, CIs for the mean will be calculated assuming a normal distribution of the data. CIs for binary endpoints will be presented using the Clopper-Pearson method. Time to event data will be analyzed both descriptively as continuous data and through Kaplan-Meier analysis. The primary study outcome of ARR over the 24-month period will be accompanied by the respective 95% CI. Sensitivity analyses of the ARR will be performed considering the relapses as count data and using a negative binomial regression model with time as explanatory variables. A zero-inflated negative binomial regression model will also be considered.
Milestones	First Patient First Visit (first patient to sign Informed Consent Form [ICF]): 31-July-2019 75 Patients Consented: 28 Feb 2020 150 Patients Consented: 30-Nov-2020 Last Patient First Visit (last patient to sign ICF): 28-Nov-2022 Last Patient Last Visit: 03-Jan-2025

	Database Lock: 17-Feb-2025 Key Stats Available: 14-Jul-2025 Clinical Study Report: 19-Sep-2025

5 Amendments and Updates

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
1	Version 2	12/11/2018	Section 3	Operational Study Lead was updated	Administrative
			Sections 4 and 9	MS-TEQ was replaced by MS-TAQ, modified versions	To adequately assess treatment adherence
2	Version 3	02/14/2019	Section 3	Operational Study Lead was updated	Administrative
			Sections 4 and 6	Dates for study milestones were updated	Administrative
			Section 11.1	Definition for severe lymphopenia was added	For added clarity
			Sections 4 and 9.2.1	Added inclusion criterion that patient must have access to a valid e-mail address	To ensure patients have a means to receive link to the PRO questionnaires
			Section 9.1.1	Updated Figure 1	For added clarity
			Sections 4 and 9.1.1	Clarified that cladribine tablets are being prescribed as per standard of care and are not given as part of this study	For added clarity
			Sections 4 and 9.1.1	Clarified that time between end of previous DMD and start of cladribine tablets is at the discretion of the investigator who should consider mode of action and duration of effect of previous DMD when making this decision	For added clarity

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
			Sections 9.1.2.4 and 9.2.4	Clarified that MRIs collected during the study follow-up period will be assessed by a central neuroradiology center	For added clarity
			Section 9.2.2	Clarified that no additional risk to patient is expected since cladribine tablets are prescribed as per standard of care and per USPI	For added clarity
			Sections 4, 9.1.1, 9.1.2.2, 9.2.4, 9.3 and 9.7.3	Clarified that treatment adherence is captured using questions that are based on MS-TAQ	For added clarity
3	Version 4	06/19/2019	Title page, Sections 4, 8.2, 9.1.1, 9.1.2.2, 9.3 and 9.7.4	Clarified that retrospective data over the 24-month period prior to enrollment should be related to patients' MS diagnosis; thus, if a patient's diagnosis is <24 months, then data since diagnosis is collected	For added clarity
			Sections 4 and 9.2.1	Changed inclusion criterion "Have time since diagnosis of RMS of at least 24 months" to "Have time since diagnosis of RMS of at least 12 months"	This inclusion criterion was updated based on site feedback and to expand the pool of eligible patients as a diagnosis of 1 year was deemed sufficient from a clinical perspective

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
			Sections 4 and 9.1.2.2	Data on all previous DMDs since MS diagnosis (rather than only those received within 2 years prior to enrollment) will be collected	Data collection on previous DMDs has been expanded for a full picture on patients' treatment pathway since MS diagnosis
			Title page, Sections 4, 7.4, 8, 8.1 and 9.2.1	Clarified that indication for cladribine tablets is RMS, including RRMS and aSPMS	For added clarity
			Title page, Sections 4, 7.4, 8.2 and 9.7.3	Re-phrased "physicians' treatment patterns" to "treatment patterns"	To clarify that MS treatment patterns are assessed, not comparisons of treatment patterns across physicians
			Section 11.1	Added further definition for severe lymphopenia to include description of Grade 3 and Grade 4 lymphopenia	For added clarity
			Section 9.1.1	Added additional recommendations from the USPI for when ALC drops to <200 cells per microliter	For added clarity
			Section 9.2.4	The time period for pre-baseline screening has been changed to -30 to 0 days (from -24 to 0 days)	To accommodate the current insurance approval and drug shipment timelines
			Section 9.3	Clarified that data on prior medication should be limited to MS symptomatic specific medications	For added clarity and to reduce site burden for data entry

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
			Section 9.1.2.2	Added information that validated Spanish translations of PROs are available for this study; except for the PDDS for which a non-validated Spanish translation is used	For added clarity and transparency regarding the PDDS Spanish translation not being linguistically validated
			Section 8.3	CCI [redacted]	To align the objective with the proposed endpoints collected in the study
			Section 9.2.4	In the schedule of assessment data collection of treatment with cladribine tablets and other MS treatment during the study was separated	For added clarity since the anticipated assessments of treatment with cladribine tablets and other MS treatment differ
			Sections 9.2.4 and 9.3	Hepatitis B and C screening was added prior to initiation of the first and second course of cladribine tablets. A footnote was included to clarify that hepatitis B screening prior to the second course of treatment with cladribine tablets is not required as per USPI if the patient received vaccination prior to the first course of treatment	For added clarity and for consistency with the USPI

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
			Section 9.2.4	Assessment of CCI was moved from the Table 1. Schedule of Assessments table to a footnote	For added clarity since CCI is only collected if assessed by the investigator as per standard of care
			Section 9.2.4	A footnote was added to Table 1. Schedule of Assessments to indicate that at PRO only time points (Month 1 and Month 13) patients will complete PROs at their home; patients are not asked to come to the clinic for PRO completion at these time points	For added clarity and to indicate reduced patient burden as PROs can be completed at home at Month 1 and Month 13
			Section 9.2.4	The column on "staff function" was removed from the Table 1. Schedule of Assessments	For added clarity since this column initially only listed the physician as being responsible for assessments at the clinic, but some of these tasks could be delegated to other site staff
			Sections 9.2.4 and 9.3	It was clarified that during study follow-up sites are asked to upload MRI scans as available per routine practice and scans will be read by a central neuroradiology center	To clarify that sites are not asked to report MRI results during follow-up
4	Version 5	8/19/2019	Section 11.1	'Pregnancy' and 'adverse pregnancy' were removed from the list of AESIs	To clarify that pregnancy and adverse pregnancy outcomes are not AESIs for this study

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
			Sections 4, 9.2.1, and 11.4	Updated inclusion criteria regarding treatment period of prior oral DMD to at least 1 month (changed from at least 3 months)	To allow enrollment of patients who might have discontinued previous oral DMD due to intolerability within less than 3 months
			Sections 4, 9.2.1, and 11.4	Updated exclusion criteria to exclude women who plan to become pregnant during cladribine treatment phase	To clarify that pregnancy is only a contraindication during the cladribine treatment phase
			Title page and Sections 4, 8.1, 9.1.1, and 9.2.1	Clarified that enrollment includes patients who are switching from infusion treatment to cladribine in addition to those previously treated with other oral DMDs	To allow enrollment of patients who are transitioning from an infusion DMD to cladribine tablets as it was observed that a substantial proportion of patients who are initiating cladribine tablets are transitioning from an infusion DMD
			Sections 4, 9.1.2.2, 9.2.4, and 9.7.3	Updated description of MS-TAQ which was also modified to assess adherence to previous infusion DMD	Since inclusion/exclusion criteria were expanded to also allow enrollment of patients transitioning from infusion DMD to cladribine tablets, the MS-TAQ had to be modified accordingly as well
			Sections 4 and 9.2.2	Updated language regarding administration of cladribine tablets to align with the USPI	To align with the USPI
			Section 9.2.4	Clarified that pregnancy, HIV, and Hep B & C assessments will be collected at Month 12	To align with the USPI

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
			Section 9.2.4	The time period for pre-baseline screening has been changed to -45 to 0 days (from -30 to 0 days)	To accommodate the current insurance approval and drug shipment timelines
			Section 9.2.4	Renamed Enrollment Visit as Baseline Visit and clarified that Baseline Visit should occur immediately prior to the patient initiating treatment with cladribine tablets and that a Screening Visit can be performed if the site anticipates a delay between decision to start cladribine and access to cladribine tablets	For added clarity
			Section 9.2.4	Definition of enrolled patient was added (i.e. once ICF is signed)	For added clarity
			Sections 4, 7.4, 8.1, 9.2.1	Abbreviated active SPMS as 'aSPMS'	Updated for consistency
			Section 9.2.5	Added statement that patients who never take at least 1 dose of cladribine tablets will be withdrawn from the study	For added clarity

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
5	Version 6	7/13/2021	Section 9.2.4	The Schedule of Assessments table notes collection of MRI documentation at the Baseline Visit, but further clarifies in footnote 'e', that during follow-up, MRIs will be assessed by a central neuroradiology center. MRI documentation, at baseline and follow-up should be sent to and reviewed by the central neuroradiology center	Updated for clarity
			Section 9.1.1 Figure 1	Figure 1 updated to reflect population including patients who have been diagnosed at least 12 months prior (previously at least 24 months). Additionally, Figure 1 was updated to reflect Table 1 (Schedule of Assessments)	Updated to align with inclusion criteria and Schedule of Assessments
			Sections 8.2, 9.2.3, 9.2.4 (Table 1), 9.7, 11.4, Section 9.1.1 (Figure 1)	Follow-up safety collection extended by 2-years	Updated to allow for the capture of long-term safety data (extending to 48 months post-treatment initiation)

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
			Sections 7.1, 7.3, 8, 8.2, 9.1.2.2, 9.2.2, 9.3, and 13	Added language incorporating patients who switch from ocrelizumab to cladribine tablets	Additional patients are being introduced to the study as a sub cohort in order to better understand clinical and/or demographic characteristics that may potentially influence the patient decision to switch from ocrelizumab to cladribine
			Sections 9.3 and 9.2.4 (Table 1)	Added capture of immunoglobulin levels (if assessed by the investigator)	Immunoglobulin levels will be collected (if monitored by investigator during routine clinical practice) for additional clinical context of the ocrelizumab cohort
			Sections 6 and 12.1	Updated study report delivery schedule and associated milestones table	Updated given safety extension
6	Version 7	7/13/2021	Sections 9.2.4, 9.3, and 9.7	Schedule of Assessments to include MRI data collection through safety extension period	Updated to ensure relevant assessments are collected as available during the safety extension time period
			Sections 9.1.1, 9.2.4, 9.3, and 9.7	PDDS assessment to be collected during the safety extension (at Month 36 and Month 48). Frequency of assessments table and Figure 1 updated accordingly to reflect change	Updated to ensure relevant assessments are collected as available during the safety extension time period

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
			Section 9.7.3	Removed 95% confidence interval metrics from secondary end point analysis presentation	95% confidence intervals will not be presented for secondary analyses given they can be wide with a reduced sample size. Further, 95% confidence intervals are not presented in the study's tables, listings, and figures and have been removed from the protocol for consistency
			Sections 9.2.4, 9.3, and 9.7	Added relapse data collection through safety extension time period	Updated to ensure relevant assessments are collected as available during the safety extension time period
			Section 9.1.1	Updated figure text to reference transition from oral/infusion medications, not injectables	Corrected from prior error
			Sections 9.1, 9.2.4, 9.3, 9.7.3, 9.7.4, and 12.1	Added footnote throughout to clarify that the last follow-up visit can occur at Month 54 if treatment is delayed	Updated for consistency
			Sections 5 and 10	Updated 'subjects' to 'patients' throughout	Updated for consistency
			Section 6	Added specific CSR addendum dates to study milestones table	Added for more precision
			Signature page	Added additional context to the PI signature page	Added to align with standard signature page language
7	Version 8	7/1/2022	Section 9.2.4: Table 1, Figure 1	Increased pre-baseline screening window to 60 days from 45	To accommodate the current insurance approval and drug shipment timelines

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
8	Version 9	9/10/2024	Section 4, Section 8.2, Section 9.1.1, Figure 1, Section 9.1.2.2, Section 9.1.2.3, Section 9.2.3, Section 9.2.4, Table 1, Section 9.3, Section 9.7, Section 9.7.3, Section 9.7.4, Section 11.4, Section 12.1	Removed 2-year safety extension and affiliated data collections items and timepoints	To accommodate early study closure as determined by Sponsor
			Section 4, Section 6	Updates to study milestones: removing safety extension period; LPI updated to actual date (28 Nov 2022) and LPO updated to 3rd Jan 2025. All subsequent milestones updated accordingly	As per Sponsors request
			Section 4	ePRO assessments and relapse information added to variables section in the protocol abstract	To provide a more comprehensive summary of variables to address the primary and secondary objectives of the study in the protocol abstract
			Cover page, Section 3, Section 4, Section 14.2	Updated to Angela Chandler, MD	As per Sponsors request
			Section 3, Section 14.2	Removed Lead PI	As per Sponsors request / Addendum provided

Amendment Number	Protocol Version	Date	Section of Study Protocol	Amendment or Update	Reason
9	Version 10	9/19/2024	Section 11.5	Contacts of the Safety Check Desk and Sponsor Safety department updated; Reporting events via Safety Check Desk clarified.	To align with the Safety Management Plan as the main operational document for safety reporting.
10	Version 11	10/21/2024	Section 14.2 Signature Page	Reinstated PI signature page erroneously removed from protocol v9.0 and subsequently missing from v10.0.	Administrative. Whilst Lead PI and requirement for Lead PI signature was removed in v9.0 onwards (see protocol addendum dated September 10, 2024), the PI protocol signature page in its entirety was erroneously removed from v9.0 and subsequently missing form v10.0. This page is still required for Site PI approval/signature of the protocol as also stated in the aforementioned addendum.

6 Study Milestones

Milestones	**Planned date**
First Patient First Visit (first patient to sign Informed Consent Form [ICF])	31-July-2019*
75 patients consented	28-Feb-2020*
150 patients consented	30-Nov-2020*
Last Patient First Visit (last patient to sign ICF)	28-Nov-2022*
Last Patient Last Visit	03-Jan-2025
Database Lock	17-Feb-2025
Key Stats Available	14-Jul-2025
Clinical Study Report	19-Sep-2025
n.b. Timelines are based on estimated date of FDA approval (01-April-2019)	
**Actual recorded dates*	

7 Rationale and Background

7.1 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 35.9 patients per 100,000 population (Walton 2020). MS median estimated prevalence varies substantially across regions, with North America and Europe presenting the highest prevalence (Multiple Sclerosis International Federation 2013). There are approximately 1,000,000 persons in the United States (US) living with MS (Wallin 2019). Regarding incidence, globally, the most recent median estimated incidence of MS is 2.5 per 100,000 person-years (Dua 2008). In the US, the incidence is estimated to be 3.2 per 100,000 person-years (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).

7.2 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 initially have a relapsing forms of multiple sclerosis (RMS) (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 RMS 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 RMS (Lublin 2014). Data on the epidemiology of highly active RMS 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) (Rudick 2006; Gold 2013) and 22.2% of treatment-naïve patients (Polman 2006) met the criteria for highly active RMS (≥2 relapses in the year prior to study entry and ≥1 gadolinium-enhancing (Gd+) lesion on T1-weighted magnetic resonance imaging [MRI] at study entry) (Polman 2006; Rudick 2006; Gold 2013).

7.3 Treatment and Management of RMS

Patients with RMS are recommended to receive treatment with disease-modifying drugs (DMDs) to decrease the rate of relapse and slow the accumulation of brain lesions on MRI. Numerous immunomodulatory agents with differing routes of administration (including injectable, oral, and infusion) and mechanisms of action have been shown to have beneficial

effects. The medications that have received labels from the US Food and Drug Administration (US FDA) for the treatment of RMS include the intravenous medications natalizumab, ocrelizumab, alemtuzumab, and mitoxantrone; the injected medications interferon beta, glatiramer, ofatumumab, and daclizumab; and the oral medications diroximel fumarate, siponimod, ozanimod, monomethyl fumarate, dimethyl fumarate, teriflunomide, fingolimod, ponesimod, and cladribine tablets. Patients with relapsing-remitting multiple sclerosis (RRMS) typically require more than one DMD during their clinical course. Because they are not curative, most DMDs are generally continued indefinitely unless they are ineffective or not tolerated. There is currently no standard protocol to guide the choice of DMD for patients with MS. Rather, treatment decisions and medication choices are the result of a thorough risk-benefit analysis and consideration of disease activity, patient-specific factors, and drug-related factors (Pardo 2017).

CCI

[redacted]

7.4 Cladribine Tablets

Cladribine (2-chloro-2'-deoxyadenosine [2-CdA]) is a synthetic anti-neoplastic drug that belongs to the subgroup of agents called purine analogs. In 2019, cladribine tablets were indicted for the treatment of patients with RMS, including RRMS and active secondary progressive multiple sclerosis (aSPMS), by the US FDA.

Three clinical trials for cladribine tablets have been completed (CLARITY, ORACLE MS and ONWARD), and data from these trials (Leist 2014; Montalban 2016; Giovannoni 2010), as well as the 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 cladribine tablets. In total, the follow-up consisted of >10,000 person-years of exposure for both cladribine tablets and placebo, with over 8 years of follow-up for some patients.

In the CLARITY trial patients with active RMS 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 (Giovannoni 2010). Treatment with cladribine tablets 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 treatment with cladribine tablets. The observed incidence rates in the monotherapy oral cohort for herpes

zoster infection were 0.86 adjusted AEs per 100 person-years for cladribine tablets 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 cladribine tablets 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 person-years (cladribine tablets 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 patients treated with cladribine tablets (incidence rates were 1.08 and 1.17 for cladribine tablets 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 tablets 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 cladribine tablets 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 tablets (e.g., lymphomas). There is no evidence of a dose effect of cladribine tablets on malignancy occurrence and with cladribine tablets, there was no change in the risk of malignancy over time. The overall malignancy rate with cladribine tablets was similar to the rates observed with other DMD approved in MS. In summary, there is no conclusive evidence for an increased risk of malignancy with cladribine tablets compared to placebo with a risk difference of 0.2033 per 100 person-years (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 DMD used in RMS (Pakpoor 2015) showed that the malignancy risk profile of cladribine tablets in the CLARITY study was comparable to that observed in similar trials with other DMD.

Data about the safety and effectiveness of cladribine tablets in real-world clinical settings are still limited since cladribine tablets were approved for treatment of adult patients with highly active RMS in August 2017 in the European Union. The product has recently been approved by the FDA in the US. Real-world data are also limited about patients' adherence to treatment with cladribine tablets, patient-reported outcomes (PROs), and treatment patterns for RMS before, during, and after treatment with cladribine tablets in patients with suboptimal response to prior oral or infusion DMDs.

8 Research Question and Objectives

The main research objectives are to evaluate the effectiveness and safety of cladribine tablets in patients with RMS, including RRMS and aSPMS, who transition to cladribine tablets after suboptimal response to any other oral DMDs or any infusion DMDs approved in the US for RMS in a real-world setting. Additionally, this study will separately describe real-world clinical and demographic characteristics among a sub-cohort of patients who transition from ocrelizumab to cladribine.

8.1 Primary Objective

To estimate the annualized relapse rate (ARR) over a 24-month period in patients with RMS, including RRMS and aSPMS, who are treated with cladribine tablets in a real-world setting and after suboptimal response to any other oral or infusion DMDs approved in the US for RMS.

8.2 Secondary Objectives

- To assess PROs, treatment adherence and treatment satisfaction during treatment with cladribine tablets

- To assess treatment patterns (MS treatment prior to transition to cladribine tablets since MS diagnosis, concomitant treatment for MS during the last 2 years prior to initiation of cladribine tablets (or since MS diagnosis, if diagnosis <24 months), follow-up treatment in case of discontinuation of cladribine tablets); and in particular, to assess the clinical and demographic characteristics related to the sequential use of ocrelizumab and cladribine

- To estimate the ARR over the 24-month period prior to initiation of cladribine tablets (or since MS diagnosis, if diagnosis <24 months)

- To collect all serious adverse events (SAEs), adverse drug reactions (ADRs), adverse events of special interest (AESI) and special situations during and following treatment with cladribine tablets over a 24-month period

CCI [redacted]

9 Research Methods

9.1 Study Design

9.1.1 Design Overview

This is a prospective, observational, multicenter, 30-month, Phase IV study. Sites in the US who are known to treat patients with MS will be targeted for enrollment. Patients who had decided prior to enrollment to transition from an oral DMD or an infusion DMD to treatment with cladribine tablets under routine clinical care and who meet all eligibility criteria consistent with the approved US Prescribing Information (USPI) will receive an initial treatment course with cladribine tablets in Year 1 and are planned to receive a second course in Year 2, as per the approved USPI. Cladribine tablets are being prescribed as part of patients' standard medical care and commercial product will be used. Patients will not be provided the cladribine tablets free of charge in connection with their participation in the study. It is expected that the investigator considered the mode of action and duration of effect of the previous DMD prior to initiation of cladribine tablets. It is at the investigator's discretion to define this time period, following respective USPI.

Baseline PROs, MRI and treatment adherence data will be collected before the first dose of cladribine tablets is taken. Baseline data on previous MS DMD use and relapses during the previous 2 years (or since MS diagnosis, if diagnosis <24 months) will be collected retrospectively at the Baseline Visit. All treatment decisions are at the discretion of the investigator. Patients will be followed up until the end of the observation period, irrespective if they discontinue cladribine tablets during follow-up.

During the observation period, patients will attend visits as per routine clinical practice, which are expected to happen approximately at the end of Months 2, 6 and 12 during Year 1, and at the end of Months 14, 18, and 24 during (i.e. after the second course of treatment during Year 2), as clinically indicated.

Post-enrollment relapse count data will be collected at Month 12 (end of Year 1) and Month 24 (end of Year 2) only. Treatment adherence data during treatment with cladribine tablets will be collected at the end of Months 1, 2, 13, and 14, while other PROs will be collected at the end of Months 6, 12 and 24[1].

Investigators are expected to assess patients' absolute lymphocyte count (ALC) in accordance with the USPI and to follow any other recommended monitoring and guidance as specified in the USPI. Based on this, investigators are expected to assess the ALC before initiating cladribine tablets in Year 1, before initiating cladribine tablets in Year 2, as well as 2 and 6 months after start of treatment in each treatment year or as clinically indicated. It is assumed that investigators will not exclusively assess the ALC, but rather the complete blood count (CBC) and, at some of these time points, also lymphocyte subsets and certain CCI [redacted] These data will be collected as available.

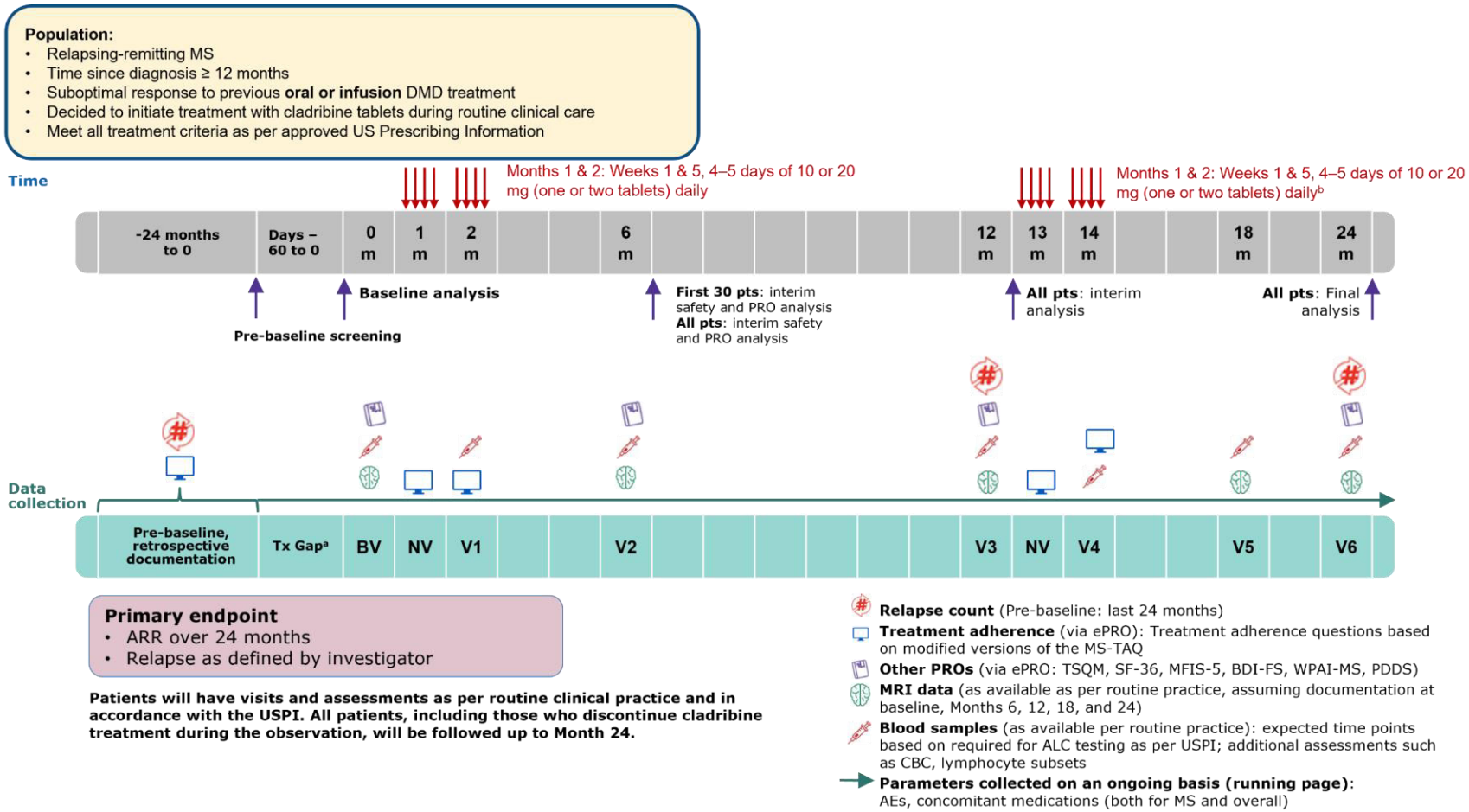
Patients with lymphopenia resulting in delay of the scheduled Year 2 treatment course are expected to receive the second treatment course once the lymphocyte count is appropriate (≥800 cells per microliter) consistent with USPI labeling and will be followed up until the end of the observation period. If the ALC drops to <500 cells per microliter, the patient should be actively monitored until values increase as per USPI. If the ALC drops to <200 cells per microliter, anti-herpes prophylaxis should be administered, and the patient should be monitored for infections. Such unscheduled additional hematology assessments as per clinical requirements should be documented as well.

An overview of the study design is shown in Figure 1.

Visits and assessments are detailed in the Schedule of Assessments (see Section 9.2.4).

[1] If Year 2 treatment is delayed, final follow up visit may occur at Month 30

Figure 1. Study Design Schematic



[a] Duration between stopping previous oral or infusion DMD and start of cladribine tablets is at the discretion of the investigator.
[b] YEAR 2 course may be delayed for some patients, according to the ALC. If Year 2 treatment is delayed, follow-up may continue through Month 30.
Note: Refer to Table 1 for more data collection details and assessments at each visit.

Abbreviations: AEs=adverse events, ALC=absolute lymphocyte count, ARR=Annualized Relapse Rate, BV=Baseline Visit, BDI-FS=Beck-Depression Inventory – Fast Screen, CBC=complete blood count, DMD=disease-modifying drug, ePRO=electronic Patient-Reported Outcome, m=month, MFIS-5=Modified Fatigue Impact Scale – 5-item version, MRI=magnetic resonance imaging, MS=multiple sclerosis, MS-TAQ=MS Treatment Adherence Questionnaire, NV=No Visit, PDDS=Patient Determined Disease Steps, PRO=Patient-Reported Outcome, pts=patients, SF-36=36-Item Short Form Health Survey, TSQM=14-Item Treatment Satisfaction Questionnaire for Medication, Tx=Treatment, US=United States, USPI=United States Prescribing Information, V=visit, WPAI-MS=Work Productivity Activity Impairment – MS.

9.1.2 Outcomes

9.1.2.1 Primary

- ARR over 24 months of treatment with cladribine tablets (prospectively collected data), accompanied by 95% CI.

For this study, a relapse will be defined as per routine clinical practice as determined by the investigator. As a guide, relapse may be defined as exacerbation of symptoms that 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.

9.1.2.2 Secondary

- Baseline scores and change in scores from baseline to Months 6, 12 and 24 for the following PROs (collected via electronic PRO [ePRO] at the practice or at the patient's home using computer's URL or device application; validated Spanish translations are available for all PROs, except for the Patient Determined Disease Steps (PDDS) scale for which a translation is used that has not been linguistically validated):
    - 14-Item Treatment Satisfaction Questionnaire for Medication (TSQM). TSQM-14 is an instrument to assess patient's satisfaction with medication, providing scores on 4 scales: side effects, effectiveness, convenience, and global satisfaction.
    - 36-Item Short Form Health Survey (SF-36). SF-36 is a self-administered, generic health status questionnaire consisting of 36 questions that measure 8 health concepts: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health.
    - Modified Fatigue Impact Scale – 5-item version (MFIS-5). MFIS-5 is a modified form of the Fatigue Impact Scale that consists of 5 questions that assess the impact of fatigue on physical, cognitive, and psychosocial functioning, with 5 response levels ranging from 0 ("Never") to 4 ("Almost always"). Total scores range from 0 to 20, with higher scores representing a greater impact of fatigue.
    - Beck-Depression Inventory-Fast Screen (BDI-FS) [7 items]. The 7 items BDI-FS is a self-report inventory for measuring the severity of depression on a 7-item scale.
    - Work Productivity Activity Impairment – MS (WPAI-MS) [6 items]. The WPAI-MS questionnaire is a validated instrument to measure impairments in work and activities. The WPAI yields 4 types of scores: 1. Absenteeism (work time missed); 2. Presenteeism (impairment at work / reduced on-the-job effectiveness); 3. Work productivity loss (overall work impairment / absenteeism plus presenteeism); 4. Activity Impairment. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

  - PDDS scale. The PDDS is a patient-reported scale to assess the disability status in patients with MS and it focuses mainly on how patients walk. A higher score represents a higher level of disability. Scores on the PDDS range from 0 (normal) to 8 (bedridden).

- Treatment adherence questions, based on modified versions of the Multiple Sclerosis Treatment Adherence Questionnaire (MS-TAQ); data to be collected via ePRO at baseline (modified for once or twice daily oral dosing to assess adherence during last previous oral DMD treatment or modified for infusion dosing to assess adherence to last previous infusion DMD treatment) and at the end of Months 1, 2, 13, and 14 (modified for cladribine tablets); a Spanish translation is available to patients.
- Proportion of patients experiencing a relapse. For this study, a relapse will be defined as determined and recorded by the investigator and information on the definition used by the investigator will be collected (see Section 9.1.2.1 for a guide on definition).
- Proportion of patients with relapse associated with hospitalization (relapse as primary diagnosis or reason for hospitalization). For this study, a relapse will be defined as determined by the investigator (see Section 9.1.2.1 for a guide on definition).
- Proportion of patients with relapse associated with glucocorticoid use. For this study, a relapse will be defined as determined by the investigator (see Section 9.1.2.1 for a guide on definition).
- Assessment of previous treatment for MS:
  - Previous DMD(s) received for MS prior to study enrollment, since MS diagnosis
  - Reasons for discontinuation of previous DMD(s)
- Assessment of clinical and demographic characteristics of patients who switch from ocrelizumab to oral cladribine tablets
  - Reasons for discontinuation of ocrelizumab
- Proportion of patients who discontinue oral cladribine tablets
  - Reason for discontinuation of cladribine tablets
  - Elapsed time to discontinuation after first dose
  - Number of doses and % of planned doses (as per USPI) received
  - Subsequent treatment chosen following discontinuation of cladribine tablets
- Assessment of concomitant MS medications used during study period
- The ARR based on the last 24 months (or since MS diagnosis, if diagnosis <24 months) prior to the start of treatment with cladribine tablets (retrospective data). For this study, a relapse will be defined as determined by the investigator (see Section 9.1.2.1 for a guide on definition).

9.1.2.3 Safety

- All SAEs, ADRs, AESIs and special situations over a 24-month period
- ALC assessed as per USPI
- CBC and lymphocyte subset information as assessed per routine clinical practice

CCI [redacted]

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. Male or female patients ≥18 years
2. Signed informed consent
3. Have diagnosis of RMS, including RRMS and aSPMS, and satisfy the approved indication for cladribine tablets as per USPI
4. Have time since diagnosis of RMS of at least 12 months
5. In the opinion of the investigator, experienced suboptimal response (lack of effectiveness, intolerability, poor adherence) to oral DMD treatment other than cladribine tablets or infusion DMD treatment
6. Had received their last previous oral DMD for at least 1 month or at least 1 dose of their last previous infusion DMD
7. Have decided to initiate treatment with cladribine tablets during routine clinical care (i.e. before enrollment)
8. Meet criteria as per the approved USPI
9. Have access to a valid e-mail address

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

1. Have been previously treated with cladribine in any dosing form (intravenous, subcutaneous, or oral)

2. Transitioning from previous oral or infusion DMD solely for administrative reasons such as relocation
3. Have any clinical condition or medical history noted as contraindication on USPI
4. Are currently participating in an interventional clinical trial
5. Pregnant or breastfeeding women, women who plan to become pregnant or men whose partner plans to become pregnant during the cladribine treatment period

9.2.2 Definition of Study Cohorts and Description of Treatments

The study will have a single primary cohort that consists of all patients enrolled in the study who received at least 1 dose of cladribine tablets. Additionally, a sub-cohort of approximately 100 patients that directly switched from ocrelizumab to cladribine tablets will be prospectively enrolled. All treatment and other medical decisions will be made by the investigator, with no directives mandated by this study protocol.

All study patients are anticipated to receive marketed cladribine tablets as per investigator discretion and as per US approved label: 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, 1 at the beginning of the first month and 1 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. Since prescribing is determined by the investigator as per standard of care and according to the USPI, the benefits and risks to patients in being in the study are not different than the benefits and risks to patients taking cladribine tablets as per standard of care and according to the USPI in the general population.

Following completion of the 2 treatment courses, do not administer additional cladribine tablet treatment during the next 2 years, as stated in the USPI.

As per USPI, ALC values need to be normal at the initiation of cladribine tablets in Year 1, and ALC results need to indicate ≥800 cells per microliter at the start of the Year 2 treatment course. If necessary, the Year 2 treatment course should be delayed for up to 6 months to allow for recovery of lymphocytes to ≥800 cells per microliter. If this recovery takes more than 6 months, the patient should not receive further treatment with cladribine tablets.

9.2.3 Observation Period

Each patient will be followed from the date of first dose of cladribine tablets until loss 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 and up to 30 months for those patients who may require a delay of initiation of Year 2 treatment for up to 6 months due to low lymphocyte counts. Follow-up will continue regardless of cladribine tablets discontinuation.

9.2.4 Frequency of Assessments

Table 1 lists the Schedule of Assessments. Patients are considered enrolled once the informed consent form (ICF) has been signed prior to any data collection for this study. The Baseline Visit is the visit immediately prior to the patient initiating treatment with cladribine tablets. If the sites anticipate a delay between the decision to start cladribine tablets and patient access to cladribine

tablets (i.e. due to delays in cladribine tablets availability or access), the site can perform a Screening Visit first to determine eligibility of the patient and a subsequent Baseline Visit closer to the time the patient starts taking cladribine tablets. Data entered during the Baseline Visit are considered baseline data for the purposes of analysis.

Sites are asked to enter patient follow-up data for up to 24 months after a patient received the initial month dose of cladribine tablets if Year 2 treatment course is not delayed, and up to 30 months after initial dose if Year-2 treatment course is delayed up to 6 months. Visits will be conducted within the context of routine clinical care; thus, the timing of study visits is approximate and not mandated by the study protocol.

It is anticipated that patients enrolled in the study may not immediately start cladribine tablets after the decision to initiate cladribine tablets is made, owing to the need to first discontinue their current oral or infusion DMD (for a time period determined by the investigator) and to potential delays in obtaining cladribine tablets in the clinical setting. The initial PRO only collection (Month 1) is intended to be obtained after the patient has started treatment with cladribine tablets. The timing of Visit 1 (Month 2) and the subsequent visits may need to be adjusted based upon the actual start date of cladribine tablets, which will be recorded by the investigator.

In accordance with the USPI, it is anticipated that patients may not receive their second course of cladribine tablets precisely 12 months after the initiation of cladribine tablets owing to ALC levels <800 cells per microliter or other potential clinical factors. In the event that the second course of cladribine tablets is delayed beyond Month 13, the PRO only collection scheduled for Month 13 should be adjusted to occur during the start of the second course of cladribine tablets. The timing of Visit 4 (Month 14) and the subsequent visits may need to be adjusted based upon the actual start date of the second course of cladribine tablets, which will be recorded by the investigator.

Table 1. Schedule of Assessments

Assessments	Data collection time points (as expected based on routine clinical practice)									
	Pre-baseline Screening Visit	**Baseline Visit** [a]	**PRO Only** [b]	**Visit #1**	**Visit #2**	**Visit #3**	**PRO Only** [b]	**Visit #4**	**Visit #5**	**Visit #6**
	(Days -60 to 0)	**Month 0**	**Month 1**	**Month 2**	**Month 6**	**Month 12**	**Month 13**	**Month 14**	**Month 18**	**Month 24**[j]
Informed consent	X									
Medical history, previous relapses, previous DMD treatment		X								
Inclusion / exclusion criteria	X									
Demographic data	X									
Pregnancy test, HIV, hepatitis B and hepatitis C and tuberculosis status		X				X				
Cladribine tablets [c]		X		X		X		X		
Other MS DMD during study period, if applicable				X		X		X		X
Neurological examination as per standard of care		X			X	X			X	X
Physical examination as per standard of care		X								
Relapse count (prospective) [d]						X				X
MRI documentation [e]		X			X	X			X	X
Hematology assessment (ALC, CBC, lymphocyte subsets, immunoglobulins) [f]		X		X	X	X		X	X	X
Patient-reported outcomes										
Treatment adherence [g]		X [h]	X	X			X	X		
TSQM		X [h]			X	X				X
SF-36		X [h]			X	X				X

Assessments	Data collection time points (as expected based on routine clinical practice)									
	Pre-baseline Screening Visit	**Baseline Visit** [a]	**PRO Only** [b]	**Visit #1**	**Visit #2**	**Visit #3**	**PRO Only** [b]	**Visit #4**	**Visit #5**	**Visit #6**
	(Days -60 to 0)	**Month 0**	**Month 1**	**Month 2**	**Month 6**	**Month 12**	**Month 13**	**Month 14**	**Month 18**	**Month 24**[j]
MFIS-5		X [h]			X	X				X
BDI-FS		X [h]			X	X				X
WPAI-MS		X [h]			X	X				X
PDDS		X [h]			X	X				X
Adverse events [i]		X		X	X	X		X	X	X
[redacted] [CCI]		[redacted]		[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]

[a] Duration between end of previous treatment and start of cladribine tablets is at the discretion of the investigator.
[b] At the PRO only time point, patients fill out the PROs at their home; patients do not come to the clinic for filling out PROs at these time points.
[c] Cladribine tablets are expected to be taken according to the USPI. If cladribine tablets are discontinued, reasons for discontinuation and follow-up MS treatment will be collected.
[d] Relapse count includes relapses associated with hospitalization and/or glucocorticoid use.
[e] For baseline MRI documentation sites are asked to record patients' most recent MRI results prior to starting cladribine tablets, which is expected to have been taken within the prior 90 days. During follow-up, MRI scans are provided as available per routine practice. MRI documentation collected at baseline and follow-up are assessed by a central neuroradiology center. Specific instructions for transfer of the MRIs to the central neuroradiology center will be provided in a separate manual.
[f] Investigators are expected to assess patients' ALC in accordance with the USPI, that is, before initiating cladribine tablets in Year 1, before initiating cladribine tablets in Year 2, and 2 and 6 months after start of treatment in each treatment year or as clinically indicated. It is assumed that investigators will not exclusively assess the ALC, but rather the CBC and, at some of these time points, also lymphocyte subsets. These data will be reported as available from routine practice. If the investigator assesses CCI [redacted], these data should be recorded as well.
[g] Treatment adherence questions, based on modified versions of the MS-TAQ, will be completed by patients via ePRO: at Baseline Visit (modified for once or twice daily oral dosing to assess adherence during last previous oral DMD treatment or modified for infusion dosing to assess adherence during last previous infusion DMD treatment) as well as at the end of Month 1, Month 2, Month 13, and Month 14 (modified for cladribine tablets).
[h] Baseline PRO scales will be completed before first cladribine tablet dose is taken.
[i] Adverse events, CCI [redacted], relapse count, PDDS score and MRI data will be collected as per running page and will be recorded on an ongoing basis as new information is collected for up to 24 months (or 30 months if treatment is delayed).
[j] If Year 2 treatment is delayed, final follow-up visit may occur at Month 30.

Abbreviations: ALC=absolute lymphocyte count, BDI-FS=Beck-Depression Inventory-Fast Screen, CBC=complete blood count, DMD=disease-modifying drug, ePRO = electronic Patient-Reported Outcome, HIV=human immunodeficiency virus, CCI [redacted], MFIS-5=Modified Fatigue Impact Scale – 5-item version, MRI=magnetic resonance imaging, MS=multiple sclerosis, MS-TAQ=Multiple Sclerosis Treatment Adherence Questionnaire, PDDS=Patient Determined Disease Steps, PRO=Patient-Reported Outcome, SF-36=36-Item Short Form Health Survey; TSQM=14-Item Treatment Satisfaction Questionnaire for Medication, USPI=US Prescribing Information; WPAI-MS=Work Productivity Activity Impairment – MS.

9.2.5 Withdrawal from the Study

Patients may discontinue from the study at any time. Investigators may choose to discontinue patients from the study at any time. Further, enrolled patients who do not take at least 1 dose of cladribine will be withdrawn from the study. The reason for any study discontinuations will be collected, if available.

9.3 Variables

The following variables will be collected:

Screening and/or Baseline Visit

- Patient demographics, including: age, sex, weight, self-reported race/ethnicity
- Date of diagnosis of MS, date of first symptoms of MS
- DMD treatments received prior to study enrollment, since MS diagnosis (including medication doses and routes of administration, start dates, stop dates, and reasons for discontinuation)
- Relapse of MS in the 2 years prior to the study period or since MS diagnosis, if diagnosis <24 months (including dates of onset and resolution of relapse)
- Most recent MRI results prior to starting cladribine tablets (baseline MRI), which is expected to have been taken within the prior 90 days[redacted]
- Results of MRI in the 2 years prior to study enrollment or since MS diagnosis, if diagnosis <24 months [redacted]
- Results of neurological examination as per standard of care (e.g., Kurtzke Functional System Scores (FSS), ambulation up to 500 meters and Expanded Disability Status Score [EDSS])
- Results of physical examination as per standard of care
- Hematology assessment (white blood cell count, hemoglobin, hematocrit, platelet count, ALC). If the investigator assesses[redacted] or immunoglobulin levels, these data should be recorded as well
- Pregnancy, human immunodeficiency virus (HIV), hepatitis B, hepatitis C and tuberculosis test results
- ePRO assessments (treatment adherence questions based on modified versions of the MS-TAQ, TSQM, SF-36, MFIS-5, BDI-FS, WPAI-MS, PDDS)
- Comorbid conditions
- List of all MS symptomatic specific medications taken in the 2 years prior to study enrollment (or since MS diagnosis, if diagnosis <24 months), including medication start and stop dates and reasons for discontinuation

Follow-Up Visits

The anticipated timing of assessments is presented in Table 1: Schedule of Assessments.

- Medication log of cladribine tablets treatment during the study period, including medication start dates, medication stop dates, medication dose (mg), number of dose and reasons for discontinuation
- Medication log containing other MS DMD treatments (if applicable) during the study period, including medication doses and routes of administration, start dates, stop dates and reasons for discontinuation
- Relapse of MS during the study period as determined by the investigator (see Section 9.1.2.1 for a guide on definition) including date of onset, resolution of relapse and definition for relapse used
- Relapse of MS associated with hospitalization (relapse as primary diagnosis or reason for hospitalization) during the study period as determined by the investigator (see Section 9.1.2.1 for a guide on definition) including date of onset, resolution of relapse and definition for relapse used
- Relapse of MS associated with glucocorticoid use during the study period as determined by the investigator (see Section 9.1.2.1 for a guide on definition) including date of onset, resolution of relapse and definition for relapse used
- MRI scans from all MRIs performed during the study period; MRI scans are assessed by a central neuroradiology center; data includes: CCI [redacted]
- Results of neurological examination as per standard of care (Kurtzke FSS, ambulation up to 5000 meters and EDSS)
- Hematology assessment (white blood cell count, hemoglobin, hematocrit, platelet count, ALC). If the investigator assesses CCI [redacted] or immunoglobulin levels, these data should be recorded as well
- Pregnancy, HIV, hepatitis B, hepatitis C and tuberculosis test results
- Comorbid conditions
- CCI [redacted]
- AEs as a continuous log
- ePRO assessments (treatment adherence questions based on modified versions of the MS-TAQ, TSQM, SF-36, MFIS-5, BDI-FS, WPAI-MS, PDDS)

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

9.4 Data Source

Data sources for this study will include data extracts from patients' medical records performed by site personnel as well as questionnaires directly filled out by patients. The data to be collected in the study will be obtained by means of an Electronic Data Capture (EDC) system. The data in the electronic Case Report Form (eCRF) should be consistent with the relevant source documents. Further details are provided in Section 9.6.

Each patient will be able to be identified from their patient file. Additionally, any other documents containing source data must be filed (e.g., laboratory value listings, etc.). Such documents must bear at least the patient number and the date when the procedure was performed. Information should be printed by the instrument used to perform the assessment or measurement, if possible. Information that cannot be printed by an automated instrument will be entered manually. Medical evaluation of such records should be documented as necessary and the documentation signed and dated by the investigator.

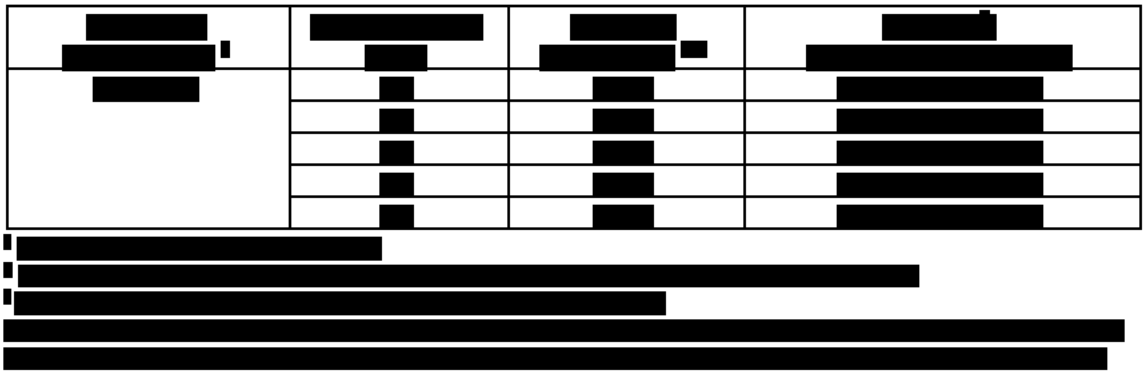
Patient questionnaire data will be recorded directly via EDC rather than entered into the patient's original medical file. In such cases there will be no record in the original patient file (either on paper or electronically) that corresponds to the entries. For all PROs, the patient will enter data directly with a validated ePRO.

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]



9.6 Data Management

The main purpose of the eCRF is to obtain data required by the non-interventional study protocol in a complete, accurate, legible, and timely manner. The data in the eCRF 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 eCRFs and any other associated documents forwarded to the Sponsor or its designated organization contain no mention of any patient names.

The data will be entered into a validated database. The Contract Research Organization (CRO) will be responsible for data processing, in accordance with the CRO's data management procedures. Database lock will occur once Quality Control and Quality Assurance procedures (including reconciliation of SAEs, ADRs, AESIs and special situations) and coding activities have been completed. PDF files of the eCRFs will be provided to the investigators at the completion of the study.

9.7 Data Analysis

Further details will be provided in a Statistical Analysis Plan.

There will be a baseline analysis and 3 interim analyses: The baseline analysis will summarize patient's baseline characteristics. In the first interim analysis, mainly for safety purposes, safety, adherence, and PRO data will be analyzed for the subset of the first 30 patients enrolled into the study at the 6-month time point. A second interim analysis on the safety, adherence and PRO data will be performed as soon as 6-month data are available for all patients. The third and full interim analysis will be performed on the 12-month data. The final analysis evaluating the primary and secondary objectives will be on the 24-month data at the end of the study.

All patients enrolled in the study who receive at least 1 dose of cladribine tablets will be included in the analyses. The primary endpoint will be analyzed at Month 24. All secondary endpoints on relapse rates, PROs, MRI, and treatment patterns will be analyzed at Month 12 (12-month interim analysis) and Month 24 (final analysis). PRO data will additionally be analyzed once the first 30 patients reach the 6-month follow-up as well as at Month 6 for all enrolled patients. Safety data

will also be assessed at Month 6 for the first 30 patients enrolled as well as at Months 12 and 24, for all patients, unless Year 2 treatment is delayed in which case the final safety assessment would occur at Month 30.

9.7.1 Analysis Sets

Full Analysis Set

The Full Analysis Set includes all patients enrolled in the study who received at least 1 dose of cladribine tablets.

Per Protocol Analysis Set

The Per Protocol Population includes all patients who have completed a full treatment course of cladribine tablets (2 weeks of treatment (4-5 doses per week) for years 1 and 2), according to the USPI and are compliant with all entry criteria.

Safety Analysis Set

The Safety Population includes all patients enrolled in the study who have received at least 1 dose of cladribine tablets (same as Full Analysis Set).

9.7.2 Derived and Transformed Data

Data will be transformed if required by the analysis method, e.g., to approximate the normal distribution of the data. Details on the eventual derivation/transformation of the analysis variables will be given in the Statistical Analysis Plan. For the primary outcome, the patterns of missingness will be explored. When the number of missing values is substantial (>5%), multiple imputation methodology will be considered for the analysis of the primary objective.

9.7.3 Statistical Methods

Descriptive statistics will be used to summarize data. If the outcome in question is a continuous variable, the number of observations, number of missing values, mean, SD, median, first quartile and third quartile, minimum and maximum values will be presented; if the outcome is categorical, numbers and percentages of patients for each of the categories and numbers and percentages of missing values will be presented.

Where appropriate, 95% CIs will be presented. For continuous data, CIs for the mean will be calculated assuming a normal distribution of the data. CIs for binary endpoints will be presented using the Clopper-Pearson method.

Time to event data will be analyzed both descriptively as continuous data and through Kaplan-Meier analysis.

Primary Endpoint Analysis:

The ARR over the 24-month period will be presented, accompanied by the respective 95% CI.

Sensitivity analyses of the ARR will be performed considering the relapses as count data and using a negative binomial regression model with time as explanatory variables. A zero-inflated negative binomial regression model will be also considered.

Secondary Endpoints Analysis:

All secondary endpoints will be analyzed at Month 12 (interim analysis) and Month 24 (final analysis). Data will be summarized descriptively.

ARR (prospective assessment): The ARR over the 12-Month and 24-Month follow-up period after starting cladribine tablets will be presented, accompanied by the respective 95% CIs.

Other relapse analyses: The proportion of patients experiencing a relapse, ARR associated with hospitalization and associated with glucocorticoid use will be presented together with the corresponding 95% CI over the 24-month and over the 12-month period.

Treatment adherence: Treatment adherence, based on modified versions of the MS-TAQ, will be described at baseline (modified for once or twice daily oral dosing to assess adherence during last previous oral DMD treatment or modified for infusion dosing to assess adherence during last previous infusion DMD treatment), and for the first and second course of treatment with cladribine tablets during the first and second treatment year (modified for cladribine tablets).

Other PROs: For each ePRO score (TSQM-14, SF-36, MFIS-5, BDI-7, WPAI-MS, and PDDS), the actual value at each visit and change in scores from Baseline to Month 6, 12 and 24[2] will be described.

Treatment patterns: Prior treatment patterns will be described at baseline (previous DMD treatment(s) and baseline characteristics of patients initiating cladribine tablets). Treatment discontinuation of cladribine tablets and the reasons for discontinuation will be described, as will be the follow-up treatments.

Annualized Relapse Rate (retrospective assessment): The ARR during the last 24 months before starting cladribine tablets (or since MS diagnosis, if diagnosis <24 months) will be presented, accompanied by the respective 95% CIs.

CCI [redacted]

CCI [redacted]

Safety: All safety data (AEs and hematology data, including lymphocyte subtype data, as available) will be evaluated descriptively.

9.7.4 Sequence of Analyses

There will be a baseline analysis, 3 interim analyses and a final analysis. Interim analyses are mainly descriptive and for monitoring purposes. Multiplicity corrections will not be considered.

- Baseline analysis: baseline characteristics of patients initiating cladribine tablets, baseline PRO data, baseline laboratory data, baseline data on previous MS DMD use, relapses during the previous 2 years (or since MS diagnosis if diagnosis <24 months), baseline MRI data and past treatment adherence will be analyzed.

- First interim analysis: safety, adherence and PRO data will be analyzed for the subset of the first 30 patients enrolled into the study at the 6-month time point. This will be conducted primarily for evaluation of safety.
- Second interim analysis: safety, adherence and PRO data will be analyzed as soon as 6-month data are available for all patients.
- Third interim analysis: full data analyses will be performed on the 12-month data for all patients.
- Final analysis: full data analyses will be performed on the 24-month data for all patients at the end of the study. The final analysis will include the endpoint analyses illustrated in Section 9.7.3 as well as a comparison of characteristics of patients completing the study vs. those who drop out.

9.8 Quality Control

This study will be monitored in accordance with the International Council for Harmonization (ICH) Note for Guidance on Good Clinical Practice (ICH Topic E6, 1996). The site Monitor will perform visits to the study site at regular intervals. Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all study-related documents and other materials at the site, including the investigator Site File, the completed Case Report Form (CRFs), and the patients' original medical records/files. The protocol, each step of the data capture procedure, and the handling of the data, including the final study report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the study to ensure the validity and integrity of the study data.

9.9 Limitations of the Research Methods

As this study is being conducted as an observational study, data will be collected in the context of routine clinical care and standard of care rather than with a mandated clinical visit and assessment completion schedule. This may lead to inconsistent and variable data collection across patients and may result in missing data or information bias. In addition, variability in the treatments received may limit interpretation of the results. However, the objectives of this study are to assess real-world effectiveness, safety, and treatment patterns of cladribine tablets and therefore an observational design is the appropriate method to achieve the study objectives.

The patients enrolled in this study may not be generalizable to all patients in the US receiving cladribine tablets for RMS. This will be addressed by including a heterogeneous group of study sites that are broadly representative of MS care centers in the US.

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 (e.g., ICF) to the responsible Independent Ethics Committee (IEC)/Institutional Review Board (IRB) for its favorable opinion/approval. The written favorable

opinion/approval of the IEC/IRB 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/IRB. The IEC/IRB 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 Patient 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/IRB before implementation in case of substantial changes.

9.10.2 Monitoring

A CRO Monitor will perform monitoring both remotely and via visits to the site at intervals. Monitoring 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

Not applicable.

9.10.4 Quality Assurance

In compliance with regulatory requirements, the Sponsor, a third party on behalf of the Sponsor, regulatory agencies, or IRB/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 patient 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 Human Patients

10.1 Patient Information and Informed Consent

An unconditional prerequisite for a patient's participation in the study is his/her written or e-signed informed consent. The patient'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 patient by the investigator before informed consent is obtained (a person designated by the investigator may give the information, if permitted by local regulations). A patient information sheet will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential patient, the investigator or his/her designee will inform the patient verbally of all pertinent aspects of the study (the language used in doing so will 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 patient and sign the ICF.

The ICF must be signed and personally dated by the patient 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 patient prior to participation.

Whenever important new information becomes available that may be relevant to the patient's consent, the written patient 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 patient in the study. The investigator will explain the changes to the previous version.

10.2 Patient Identification and Privacy

A unique patient number will be assigned to each patient at inclusion. This number will serve as the patient's identifier in the study as well as 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 patient names are included on copies of documents submitted to the Sponsor, the names (except for initials) must be obliterated and the assigned patient 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 ICFs, 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 patient'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 patient 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

An AE is any untoward medical occurrence in a patient or clinical study patient 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

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, 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 ADR will not be submitted to the authorities as Individual Case Safety Reports. They will be collected and considered in the study report or any interim reports, as applicable.

Serious Adverse Events/Serious Adverse Reaction

An SAE/ Serious Adverse Reaction (SAR) 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 judgment 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 jeopardize 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 terms list is intended to be used for assessment of suspected ADRs (see EMA/207865/2017).

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

Adverse Event of Special Interest

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 following events will be considered AESIs:

- Severe lymphopenia: defined as Grade 3 (<500 to 200 cells per microliter) or Grade 4 (<200 cells per microliter)
- Severe infection
- Tuberculosis
- Herpes zoster infection
- Progressive multifocal leukoencephalopathy
- Other opportunistic infection
- Malignancy

Events that Do Not Meet the Definition of a Serious Adverse Event

Elective hospitalizations (e.g., an overnight stay to facilitate therapy) are not considered as SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (e.g., undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as Adverse Events

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

In this protocol, symptoms and signs of relapse or worsening of MS will be captured in the context of the effectiveness assessment and recorded on the relapse module of the eCRF. Therefore, symptoms, relapses or worsening of MS will not be considered as AEs nor captured on the AE module of the eCRF unless suspected to be related to cladribine tablets (i.e., worsening is not consistent with the anticipated natural progression of the disease).

11.2 Severity of Adverse Events

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

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

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

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

11.3 Causality Assessment of Adverse Events

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 ADRs), the patient's condition (medical history, underlying disease), CCI , 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 patient is initially included in the study (date of signature of first informed consent) and continues at least to the end of the follow-up period (i.e. up to 24 months in most patients or up to 30 months in patients with delayed start of Year 2 treatment).

All safety data, as specified above (SAEs and AESI), occurring during the study, must be documented by the investigator within 24 hours of awareness and recorded in the CRF, 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 ADRs/AEs. Therefore, the primary cause of death, disability or hospitalization should be recorded and reported as an SAE/ADR, 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 in Section 11) 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 data collection forms for pregnancy, independent if an AE was reported or not (this includes male patients whose partner becomes pregnant during the cladribine treatment period). The outcome of the pregnancy should be followed up and reported to the Sponsor until delivery. In the event of a pregnancy occurring during the cladribine treatment period, the female patient must be discontinued from cladribine tablets immediately.

Request for immediate discontinuation of study drug. In accordance with the USPI, patients should discontinue cladribine tablets if they become pregnant during the cladribine treatment period, become infected with HIV, develop an active chronic infection (hepatitis or tuberculosis) or develop moderate or severe renal impairment (creatinine clearance <60 milliliter per minute).

11.5 Safety Data Collection for Reporting

Safety Data Collection Forms:

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

- (S)AE Report Form
- Pregnancy Report Form
- Parent-Child/Fetus AE Report Form
- AESI Report Form

Reportable Events

The following events are reportable to the PPD PPD PPD (Safety Check Desk) (via Fax: PPD or E-PPD within 24 hours of awareness:

- All SAEs (related or unrelated) are to be reported independent of their relationship to the study drug by entering the event onto the eCRF or via the SAE paper report form in the event of eCRF outage
- AESIs should be reported if non-serious via the eCRF or via the AESI paper reporting form in the case of an eCRF outage and if serious following the procedure for an SAE, as described
- Non-serious ADRs are to be reported within 4 calendar days via the eCRF directly to the Sponsor Global Patient Safety (contact below), or via the ADR paper reporting form in the case of an eCRF outage

- Pregnancy or lactation is to be reported by entering the event of pregnancy on to the relevant eCRF pages in conjunction with completing and sending the Pregnancy Report Form
- All events that occur in a Child/Fetus of a pregnant woman who was exposed to the study drug are to be reported via the eCRF or via the paper reporting form in the case of an eCRF outage
- Special situations (see definition in Section 11, including pregnancy, overdose, off-label use, misuse, medication error, occupational exposure, lack of therapeutic effectiveness) should be reported on the (S)AE Report Form by indicating whether serious or not

All reportable events shall be reported via the Safety Check Desk, except for NSADRs that shall be reported directly to GPS.

Procedure for Safety Data Reporting (Completion and Forwarding)

For any new events that are serious, fatal or related to a special situation the investigator/healthcare provider must immediately (within 24 hours after becoming aware of the event) report the event via the eCRF or via the paper reporting form in the case of an eCRF outage. For all events that are non-serious an electronic data transfer (or paper form in case of eCRF outage) must be transmitted within 4 calendar days to Sponsor, including the PPD PPD PPD if applicable. 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 Lifecycle Safety (Safety Check Desk):

- E-mail:PPD
- Fax: PPD

Global Patient Safety:

- E-mail: PPD
- Fax: PPD

The data entered on the safety data collection forms must be consistent with the information recorded in the CRF. 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
- Patient 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 related to cladribine tablets 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 patient is withdrawn from the study. If an abnormal outcome occurs, the respective safety data collection form (Pregnancy Report Form, Parent-Child/Fetus 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, special situations and AESIs occurring during the study must be monitored and followed up by the investigator until stabilization or until the outcome is known, unless the patient 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, special situations and AESIs, missing information such as outcome, confounders, and causality are to be provided. Additionally, follow-up information of non-serious ADRs 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.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

No scheduled laboratory assessments are required by protocol. Nevertheless, laboratory data of medical importance, as deemed necessary and requested by the investigator as part of the patient's standard medical care, will be, when available, recorded into the eCRF by the investigator.

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an electrocardiogram trace) should not be reported as AEs unless they are associated with clinical signs and symptoms or are considered otherwise medically important by the investigator or general

practitioner. If an abnormality fulfills these criteria, the identified medical condition (e.g., anemia, increased alanine transaminase [ALT]) must be reported as the AE rather than the abnormal value itself.

Vital Signs, Physical Examinations, and Other Assessments

Weight will be collected at baseline when available.

Physical examination data will be collected during the course of routine clinical care. Abnormal physical examination findings should not be reported as AEs unless they are considered medically important by the investigator. If an abnormality fulfills these criteria, the identified medical condition must be reported as the AE rather than the abnormal physical examination finding itself.

11.6 Regulatory Reporting to the Health Authorities

Expedited reporting of SAEs and non-serious ADRs to Health Authorities is performed by the Sponsor's Local Patient Safety Officer (LPSO) 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 (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 first and second interim reports will present the results of analyses of the safety, adherence, and PRO data. These reports will allow interim assessment of the safety of cladribine tablets in this study.

The third interim report will present results of the analysis of the safety, adherence, and PRO data, as well as the analyses of the primary and secondary outcomes at 12 months. This report will allow interim assessment of all relevant aspects of the study.

The completed study will be summarized in a final clinical study report (CSR) that accurately and completely presents the study objectives, methods, results, limitations of the study, and interpretation of the findings from study start through Month 24.

12.2 Publication

The study design as well as yearly interim data will be presented at scientific congresses. The first publication will include the results of the analysis of the primary outcome(s) and 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.

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14 Appendices

14.1 List of Stand-Alone Documents

Not applicable.

14.2 Signature Pages and Responsible Persons for the Study

Signature Page – Protocol Lead

Study Title:	Cladribine tablets: Observational evaluation of effectiveness and patient-reported outcomes (PROs) in subopti<u>MA</u>lly controlled patient<u>S</u> previously <u>T</u>aking oral or infusion dis<u>E</u>ase-modifying d<u>R</u>ugs (DMDs) for relapsing forms of multiple sclerosis (RMS) (MASTER-2)
Study Protocol Date / Version:	21 October 2024 / Version 11.0
Protocol Lead Responsible for Designing the Non-interventional Study:	PPD

I approve the design of the non-interventional study:

_____ _____

Signature Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	EMD Serono, Inc. A business of Merck KGaA, Darmstadt, Germany
Address:	One Technology Place Rockland, MA 02370, USA
Telephone number:	PPD
Fax number:	n/a
E-mail address:	PPD

Signature Page – Principal Investigator

Study Title	Cladribine tablets: Observational evaluation of effectiveness and patient reported outcomes (PROs) in subopti<u>MA</u>lly controlled patient<u>S</u> previously <u>T</u>aking oral or infusion dis<u>E</u>ase-modifying d<u>R</u>ugs (DMDs) for relapsing forms of multiple sclerosis (RMS) (MASTER-2)
Study Protocol Date / Version	21 October 2024 / Version 11.0
Center Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the study at this site. 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.

_____ _____

Signature Date of Signature

Name, highest 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:	EMD Serono R&D Center, Inc
Address:	PPD 821
Telephone number:	PPD
E-mail address:	PPD

Protocol Amendment (Study Level) - v11.0 - 26-Oct-2024

Electronic Signature Manifestation

This page is a manifestation of the electronic signature(s) used in compliance with the organization's electronic signature policies and procedures.

Signer Full Name	Meaning of Signature	Date and Time
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	26 Oct 2024 19:34:06 UTC

PPD