Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A 2-year extension study to evaluate long-term effectiveness of Mavenclad® in participants who have completed Trial MS700568_0022 (MAGNIFY MS)
Study Number:	MS700568_0157
Amendment Number:	Not Applicable
Merck [Compound]**:**	Mavenclad®
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	IV
Short Title:	Extension to the MAGNIFY MS trial on Mavenclad®
Acronym or Abbreviation:	Magnify MS Extension
Coordinating Investigator:	PPD
Sponsor Name and Legal Registered Address:	**Sponsor**: Affiliates of Merck KGaA, Darmstadt, Germany Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250 Darmstadt, Germany **Medical Responsible:** PPD

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A 2-year extension study to evaluate long-term effectiveness of Mavenclad® in participants who have completed Trial MS700568_0022 (MAGNIFY MS)

Short Title: Extension to the MAGNIFY MS trial on Mavenclad®

Rationale: Despite the recent approvals of several newer therapies, the treatment burden of multiple sclerosis (MS) remains significant. While the randomized control studies on cladribine tablets (Mavenclad®) provide a wealth of information on clinical and safety outcomes, studies evaluating its long-term effect (over 2 years after initial treatment) are relatively limited. This study is designed to collect long-term efficacy and safety data of participants with highly-active relapsing multiple sclerosis (RMS) treated with cladribine tablets.

Objectives and Endpoints: The primary and secondary objectives and endpoints are provided in Table 1.

Table 1: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the long-term disease activity during Year 3 and 4 after initial dose of cladribine tablets	Proportion of participants with No Evidence of Disease Activity (three parameter [NEDA-3]) during Year 3 and 4 after the initial dose of cladribine tablets
Secondary	
To further explore the long-term treatment effect of cladribine tablets	• Proportion of participants with NEDA-3 during Year 3 after the initial dose of cladribine tablets • Proportion of participants with NEDA-3 during Year 4 after the initial dose of cladribine tablets • Proportion of participants with NEDA-3 after the onset of action of cladribine treatment during the parent study until the end of Year 3 after the initial dose of cladribine tablets • Proportion of participants with NEDA-3 after onset of action of cladribine treatment during the parent study until the end of Year 4 after the initial dose of cladribine tablets • Proportion of participants remaining NEDA-3 during Year 3 or 4 after the initial dose of cladribine tablets among those with NEDA-3 during Year 1 or 2 after the initial dose of cladribine tablets

	• Time to first disease activity, defined as the time to first occurrence of either qualifying relapse, or confirmed disability progression (CDP), or new or enlarging T2-hyperintense lesions, or new T1 gadolinium enhancing (Gd+) lesions, during Year 3 and 4 after initial dose of cladribine tablets
	• Time to first disease activity, defined as the time to first occurrence of either qualifying relapse, or CDP, or new or enlarging T2-hyperintense lesions, or new T1 Gd+ lesions, over 4 years after the initial dose of cladribine tablets (i.e., between initial dose and end of the extension study)
	• Time from the initial dose of cladribine tablets to
	  • first new or enlarging T2 lesion
	  • first new T1 Gd+ lesion
	  • first CDP, as measured by Expanded Disability Status Scale (EDSS)
	  • first qualifying relapse
	  • second qualifying relapse
	  • treatment start with other disease modifying drugs (DMDs)
	• Time from extension study baseline to
	  • first new or enlarging T2 lesion
	  • first new T1 Gd+ lesion
	  • first CDP, as measured by EDSS
	  • first qualifying relapse
	  • second qualifying relapse
	  • treatment start with other DMDs

To evaluate long-term safety of cladribine tablets	Occurrences of adverse events (AEs) and serious adverse events (SAEs) during Year 3 and 4 after the initial dose of cladribine tablets

AE: Adverse Event; CDP: Confirmed Disability Progression; DMD: Disease Modifying Drug; EDSS: Expanded Disability Status Scale; Gd+: Gadolinium Enhancing; NEDA-3: Three parameter No Evidence of Disease Activity; SAE: Serious Adverse Event.

Overall Design: This will be an extension study to the 2-year MAGNIFY MS trial (i.e., parent study) to observe participants in Year 3 and 4 after the 2-year treatment with cladribine tablets; no cladribine tablets will be administered during the extension study period. Participants will attend visits for assessments at extension study Baseline, which is planned to coincide with the last visit of the parent study at 12 months after initiation of the second year cladribine treatment (or 24 months after initiation of first year treatment if the participant did not initiate the second year treatment); for participants who complete the parent study before the recruitment is open for the extension study, the extension study Baseline visit may be planned later, after the parent study last visit and before Visit 1. For these patients, data will be collected retrospectively from the potential gap period between the parent study last visit and the extension study Baseline. In addition, participants will attend Visit 1 (at Month 12/Year 1 since parent study last visit) and Visit 2 (at Month 24/Year 2 since parent study last visit). The study includes 3 sub-studies, which include additional sample collection from participants who agree to participate.

Disclosure Statement: This will be an open label, single arm, exploratory, multicenter, 2-year, retrospective and prospective, Phase IV extension study. The primary purpose is the evaluation of long-term disease activity after treatment with cladribine tablets in adults with highly-active RMS. No cladribine tablets will be administered during the study, but the study has an interventional nature due to mandated visits and assessments (including MRIs and blood draws).

Number of Arms: 1.

Blinding: Not applicable.

Number of Participants: A maximum of 256 participants are planned to be enrolled to obtain 200 to 220 evaluable participants.

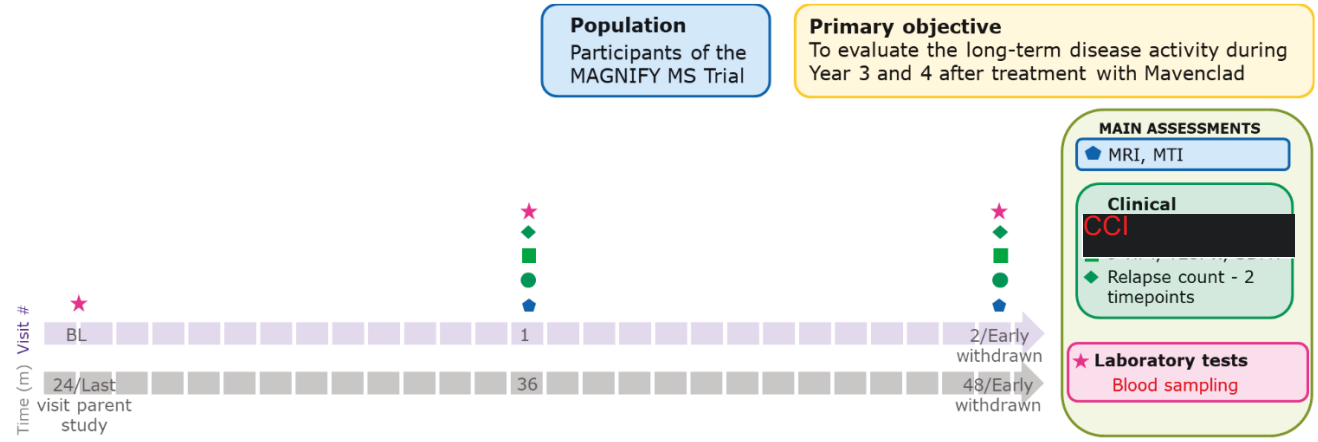
Study Intervention Groups and Duration: The extension study will cover a 2-year period in which the participants will not be administered cladribine tablets, which was administered during the parent study. Participants will be followed up for 2 years.

Involvement of Special Committee(s): Yes.

1.2 Schema

A schema of the study design is presented below (Figure 1).

Figure 1: Study Schema



CCI; BL: Baseline; EDSS: Expanded Disability Status Scale; MRI: Magnetic resonance imaging; MTI: Magnetization transfer imaging; CCI

Note: The extension Baseline is planned to coincide with the parent study last visit (Month 24 visit of MAGNIFY MS trial). For participants who completed the parent study before the recruitment is open for the extension study, the Baseline visit will be planned later (after the parent study last visit and before Visit 1). Visit 1 is planned 12 months (± 30 days) after the parent study last visit and Visit 2 is planned 24 months (± 30 days) after the parent study last visit (for further details, see Section 4.1).

1.3 Schedule of Activities

The order of the assessments is as provided in the Schedule of Activities (Schedule of Activities) (Table 2).

Table 2: Schedule of Activities

Assessments & Procedures	Assessment Period				Notes
	Extension Baseline	Visit 1	Early withdrawal / Visit 2	Unscheduled visits	
Study month		12	24	Baseline Visit-24	
Visit window		± 30 days	± 30 days		
Informed consent	X				Informed consent should be obtained prior to any study-specific assessments.
Inclusion/exclusion criteria	X				Enrollment will be done after the confirmation of fulfilling all inclusion criteria without matching any exclusion criteria.
Demography	X				
Concomitant medications and procedures	X	X	X	X	Baseline: Collected retrospectively for potential gap period (see Section 4.1).
MRI					
Magnetic Resonance Imaging (MRI), CCI [redacted]		X	X		
Disability					
Disability: Expanded Disability Status Scale (EDSS)/ CCI [redacted]	X	X	X	X	Baseline: Retrospective data collection of any EDSS performed during the potential gap period (see Section 4.1). Unscheduled visits: Required if relapse is suspected (see Section 4.1).
CCI [redacted]		[redacted]	[redacted]		
[redacted]		X	X		
CCI [redacted]					
[redacted]		X	X		
Relapse reporting	X	X	X	X	Baseline: Retrospective data collection for potential gap period (see Section 4.1). Unscheduled visits: Required if relapse is suspected (see Section 4.1).
Collection and review of patient diary		X	X	X	To be captured into the respective electronic case report forms (eCRFs) from patient diary in case of any entry at home.
Safety Assessments					
Adverse event reporting	X	X	X	X	Also captured in patient diary when at home. Baseline: Collected retrospectively for potential gap period (see Section 4.1).

Assessments & Procedures	Assessment Period				Notes
	Extension Baseline	**Visit 1**	**Early withdrawal / Visit 2**	**Unscheduled visits**	
Study month		12	24	Baseline Visit-24	
Visit window		± 30 days	± 30 days		
Physical examination		X	X	X	
Vital signs		X	X	X	
Medical history	X				Only serious adverse events (SAEs) and lymphopenia (also if not serious) which are ongoing since the parent study (see Section 8.3.1)

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Assessments & Procedures	Assessment Period				Notes
	Extension Baseline	Visit 1	Early withdrawal / Visit 2	Unscheduled visits	
Study month		12	24	Baseline Visit-24	

CCI [redacted]

CCI [redacted] CSF: Cerebrospinal fluid; DMD: Disease Modifying Drug; eCRF: Electronic Case Report Form; EDSS: Expanded Disability Status Scale; CCI [redacted]

CCI [redacted] SAE: Serious Adverse Event; CCI [redacted]

2 Introduction

Mavenclad® (cladribine tablets) was approved (European Medicines Agency approval on 25 August 2017) for the treatment of highly-active relapsing multiple sclerosis (RMS) in adults. Detailed information on the chemistry, pharmacology, efficacy, and safety of Mavenclad is in the Summary of Product Characteristics (SmPC).

2.1 Study Rationale

Despite the recent approvals of several newer therapies, the treatment burden of multiple sclerosis (MS) remains significant. While the randomized control studies on cladribine tablets provide a wealth of information on clinical and safety outcomes, there is a call for Phase IV studies to monitor long-term effects of sequential disease-modifying therapies (Derfuss 2020). This study adds to the evidence by investigating the long-term efficacy and safety effects (over the third and fourth year after initiation of treatment) among adults with highly-active RMS.

This extension study will collect follow-up data from the MAGNIFY MS trial (i.e., the parent study) until 4 years after the initial dose of cladribine tablets to explore the long-term effects of cladribine tablet administration.

See Section 4.2 for further details on the study rationale.

2.2 Background

Multiple sclerosis is a chronic, inflammatory, progressive, demyelinating disease of the central nervous system and is the most common cause of serious neurological disability in young adults (Przybek 2015). The disease course of MS is heterogeneous and unpredictable requiring chronic treatment and regular medical monitoring by numerous methods such as magnetic resonance imaging (MRI) that was designed for the investigation, diagnosis, and management of patients with MS (Oreja-Guevara 2015).

Eight percent of patients with MS experience a highly-active disease course with a rapid disability often heralded by high relapse rates and early motor, cerebellar and/or cognitive dysfunction (Hirst 2008). Early initiation of effective immunotherapy is considered to be important in this group of patients in order to prevent aggressive disease progression and severe disability accumulation (Dubey 2015).

It has been demonstrated that treatment with cladribine tablets in 2 short courses over 2 consecutive years has consistently shown robust clinically and statistically significant benefits in patients across the spectrum of Relapsing Remitting MS (RRMS) (early to late stages, treatment naïve, or experienced patients) (Giovannoni 2010; Leist 2014). In particular, it was found that treatment with cladribine tablets resulted in significant improvements in clinical and radiological efficacy outcomes, with significantly more patients remaining free from relapse, free from 3-month sustained Expanded Disability Status Scale (EDSS) progression, and free from MRI lesion activity over 96 weeks compared to placebo (Giovannoni 2010).

Cladribine tablets are indicated for the treatment of adult patients with highly-active RMS as defined by clinical or imaging features:

- patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs (DMDs),

- patients with 2 or more relapses in the previous year, whether on DMD treatment or not.

Efficacy data from the CLARITY trial, a Phase III, placebo-controlled, double-blind study, showed a statistically significant lower annualized relapse rate (ARR), higher proportion of participants relapse-free over 96 weeks, higher proportion of participants free of sustained disability over 96 weeks, and increased time to 3-month EDSS progression in participants receiving cladribine 3.5 mg/kg compared to participants on placebo (Giovannoni 2010). In addition, cladribine was statistically significantly superior to placebo with regard to the number and relative reduction of T1 Gd+ lesions, active T2 lesions, and combined unique active (CUA) lesions as demonstrated in brain MRI over the entire 96 weeks of the study (Comi 2013).

2.3 Benefit/Risk Assessment

The purpose of this study is to assess the long-term effectiveness of cladribine tablets over the third and fourth year after the initial administration of cladribine tablets. Results from this study may be of benefit to patients with MS and clinicians by helping to inform future treatment approaches and treatment decision-making. The benefits of increased potential convenience and compliance with the unique posology of cladribine tablets will fill an unmet medical need in treating subjects with MS.

Cladribine tablets is an oral drug approved in the treatment of highly-active RMS. Data from the CLARITY trial results suggest a clear benefit over placebo underlining the rationale for earlier treatment with cladribine tablets. In addition, data from CLARITY extension study indicates that treatment with cladribine tablets over 2 years, followed by 2 years of a placebo, produces a durable clinical response (as measured from the end of CLARITY to the end of the extension period). Importantly, there was no evidence of increased clinical activity (i.e., disease rebound) after treatment discontinuation (e.g. in the cladribine 3.5 mg/kg switched to the placebo group), as reported for other therapies in MS with a direct effect on lymphocytes (Giovannoni 2018; Giovannoni 2019). The 2-year CLARITY trial and CLARITY extension study also demonstrated the safety and tolerability of cladribine tablets in RRMS (Cook 2016). More detailed information about the known and expected benefits and risks and reasonably expected adverse events of cladribine tablets may be found in Section 4.2 and the SmPC.

The risk-benefit relationship was carefully considered in the planning of this extension study. Minimal risk to patients is expected since patients enrolled in this study will not be receiving cladribine tablets; the cladribine treatment course is to be completed under the study protocol of the parent study, and the participants will receive routine clinical care over the extension study period. This extension study will involve mandated visits and assessments as per the study protocol. Although most assessments are also part of routine monitoring of MS disease progression and treatment outcomes, this extension study will be of an interventional nature due to the mandated assessments including MRIs and blood draws. These additional diagnostic or monitoring procedures do not pose more than minimal risk or burden to the safety of the participants compared to normal clinical practice.

The MRI scans are part of the study assessments. The MRI scanning with gadolinium enhancing contrast agents is routinely used for the identification and characterization of MS lesions

(Rovira 2012). A recent assessment by European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) concluded on the positive benefit risk outcome on gadolinium agents (gadobutrol, gadoteric acid and gadoteridol) with a recommendation to continue the use of such agents as per their current indications (EMA/424715/2017).

The study assessments include the analysis of blood samples. Blood draws may cause discomfort, bruising and very rarely infection at the site where the skin is punctured by the needle. Participants may also experience dizziness, nausea, or fainting during blood sampling. However, in general, these reactions are mild to moderate and will resolve on their own.

Based on the available clinical and safety data to date, the conduct of the study, as specified in this protocol, is considered justifiable.

This extension study will be conducted in compliance with the clinical study protocol, International Council for Harmonization (ICH) Good Clinical Practice (GCP) and any additional applicable regulatory requirements.

3 Objectives and Endpoints

The study objectives and their linked endpoints are described in Table 3. Statistical analyses of the endpoints are described in Section 9.4.

Table 3: Study Objectives

Objectives	Endpoints
Primary	
To evaluate the long-term disease activity during Year 3 and 4 after initial dose of cladribine tablets	Proportion of participants with No Evidence of Disease Activity (three parameter [NEDA-3]) during Year 3 and 4 after the initial dose of cladribine tablets
Secondary	
To further explore the long-term treatment effect of cladribine tablets	• Proportion of participants with NEDA-3 during Year 3 after the initial dose of cladribine tablets • Proportion of participants with NEDA-3 during Year 4 after the initial dose of cladribine tablets • Proportion of participants with NEDA-3 after the onset of action of cladribine treatment during the parent study until the end of Year 3 after initial dose of cladribine tablets • Proportion of participants with NEDA-3 after onset of action of cladribine treatment during the parent study until the end of Year 4 after the initial dose of cladribine tablets • Proportion of participants remaining NEDA-3 during Year 3 or 4 after the initial dose of cladribine tablets among those with NEDA-3 during Year 1 or 2 after the initial dose of cladribine tablets • Time to first disease activity, defined as time to first occurrence of either qualifying relapse, or confirmed disability progression (CDP), or new or enlarging T2-hyperintense lesions, or new T1 gadolinium enhancing (Gd+) lesions, during Year 3 and 4 after the initial dose of cladribine tablets • Time to first disease activity, defined as time to first occurrence of either qualifying relapse, or CDP, or new or enlarging T2-hyperintense lesions, or new T1 Gd+ lesions, over 4 years after the initial dose of cladribine (i.e., between the initial dose of cladribine tablets and end of the extension study)

Objectives	Endpoints

	• Time from the initial dose of cladribine tablets to
	  • first new or enlarging T2 lesion
	  • first new T1 Gd+ lesion
	  • first CDP, as measured by Expanded Disability Status Scale (EDSS)
	  • first qualifying relapse
	  • second qualifying relapse
	  • treatment start with other disease modifying drugs (DMDs)
	• Time from extension study Baseline to
	  • first new or enlarging T2 lesion
	  • first new T1 Gd+ lesion
	  • first CDP, as measured by EDSS
	  • first qualifying relapse
	  • second qualifying relapse
	  • treatment start with other DMDs

To evaluate the long-term safety of cladribine tablets	Occurrences of adverse events (AEs) and serious adverse events (SAEs) during Year 3 and 4 after initial dose of cladribine tablets

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4 Study Design

4.1 Overall Design

This will be an open label, single arm, multicenter, retrospective and prospective, 2-year Phase IV extension study of the MAGNIFY MS trial (EudraCT no.: 2017-002631-42).

The parent study (MAGNIFY MS trial) is a single arm, open label, multicenter, 2-year Phase IV study of participants who received treatment with cladribine tablets for 2 years, with one treatment course of 2 weeks each year. Baseline is defined as the day on which the first dose of cladribine tablets was administered.

This extension study involves a 2-year follow-up of participants who completed the parent study. Participants who early withdrew or were withdrawn from treatment with cladribine tablets in the parent study may participate in the extension study. The follow-up period will cover Year 3 and 4 after initial administration of cladribine tablets. During this follow-up period, participants will not be treated with cladribine tablets.

Extension Baseline: The extension Baseline is planned such that it coincides with the last study visit of the parent study (i.e., Month 24 Visit of the parent study). The parent study last visit is planned at 12 months after initiation of the second-year treatment with cladribine tablets (or 24 months after initiation of first year treatment if the participant did not initiate the second-year treatment). For participants who complete the parent study before recruitment is open for the extension study, the extension Baseline visit will be planned later, after the parent study last visit and before Visit 1. For these participants, there will be a gap period between the parent study last visit and extension Baseline. Extension Baseline will involve retrospective data collection for the participants with a gap period between the parent study last visit and extension Baseline, to record any EDSS assessments, relapses, any adverse events (AEs) and serious adverse events (SAEs) (see Section 8.3.1), and concomitant medications (see Section 6.5) that may have been performed/initiated in that time period.

Visit 1 and Visit 2: Visit 1 is planned 12 months (Year 1) after the parent study last visit and Visit 2 is planned 24 months (Year 2) after the parent study last visit. The visits should be planned as close to the yearly date as possible, but as a maximum, fall within a window of ±30 days. Visit 1 and 2 are planned relative to parent study last visit; therefore, participants with a gap period between the parent study last visit and extension Baseline will have less than 12 months between the extension Baseline and Visit 1 and less than 24 months between extension Baseline and Visit 2.

Early Withdrawal: In the event of early discontinuation from the extension study, the participants will be invited for an Early Withdrawal visit as soon as possible. Visit schedules for efficacy and safety assessments are detailed in the Schedule of Activities (Section 1.3). In case the participant is not willing or cannot return to the site for the Early Withdrawal visit, a telephone call will be organized to obtain the reason for withdrawal and AEs reporting.

Unscheduled visits: A participant may return for an unscheduled visit at the discretion of the Investigator and these visits may include assessments as described in the Schedule of Activities (Section 1.3). If a participant experiences a relapse requiring treatment with steroids or switching to other DMD, a blood sample will be taken before administration of these drugs, irrespective of

time left for the next scheduled visit and blood sample collection, and irrespective of participant continuing or discontinuing the study. Further assessments and management of relapse are at the discretion of the physician.

The data from scheduled and unscheduled visits will be collected in the electronic case report form (eCRF).The schema and visit schedules for efficacy and safety assessments are detailed in the study schema (Section 1.2) and the Schedule of Activities (Section 1.3).

The planned study duration for each participant is 2 years (see Section 1.2). The study aims to enroll the first patients in Q1 2021 and have the Last Patient Last Visit in Q4 2023.

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A Scientific Steering Committee (SC) will be established to ensure that the study meets scientific standards (Appendix 2 Study Governance); this will be the same SC as in the parent study. The SC charter will be in place that describes the SC responsibilities. The SC is a multidisciplinary group of lead study Investigators, medical experts, and Sponsor's personnel, who, collectively, have the scientific, medical, and clinical study management experience to design, conduct and evaluate the study. The SC provides advice and recommendations regarding the design, conduct, and evaluation of the study. The SC is responsible for safeguarding the interests of participants and for the conduct of the study.

4.2 Scientific Rationale for Study Design

The purpose of this study is to explore the long-term effectiveness of cladribine tablets, in terms of disease activity and safety, in patients with highly-active RMS previously participating in the MAGNIFY MS trial.

While clinical studies have demonstrated evidence for the efficacy of new therapies for MS, these studies are often of a limited duration and may not capture long-term outcomes (Lucchetta 2020). Long-term studies are needed to establish the clinical benefits and safety of new drugs in MS patients. This extension study of the MAGNIFY MS trial will contribute to the knowledge on the long-term effect of cladribine tablets for the third and fourth year after initiation of treatment.

Treatment with cladribine tablets has a maximum duration of 20 days in 2 years, after which patients are monitored for an additional 2 years (treatment-free). The design of this study is based on visits that are part of routine clinical practice.

Significant differences in freedom from disease activity between the cladribine and placebo groups have been previously noted as early as 24 weeks. About two-thirds of patients treated with cladribine who were free from disease activity at 24 weeks after initiating treatment, and more than 80% of patients treated with cladribine who were free from disease activity at 48 weeks, remained free from disease activity at 96 weeks. This suggests that freedom from

disease activity at these earlier timepoints (before retreatment with cladribine tablets starting at Week 48) is a good predictor of freedom from disease activity at the end of the study; however, by its nature, this type of analysis enriches for a responder population (Giovannoni 2011). The current extension study will evaluate the long-term effects of cladribine tablets on freedom from disease activity.

The MRI is a sensitive, non-invasive approach to imaging the brain and spinal cord and is the preferred method of imaging to diagnose and monitor MS. The MRI based measures are of paramount relevance due to their sensitivity in detecting and quantifying the focal and diffuse pathology occurring in MS. The MRI measures of white matter lesional activity (i.e., new/enlarging T2 lesions or Gd+ T1 lesions) and those of brain atrophy (i.e., percentage of brain volume change) have shown to be valid surrogate endpoints for clinical outcomes (Sormani 2014).

In the present extension study, the long-term disease activity will be defined by no evidence of disease activity (NEDA), also referred to as freedom from disease activity. This is a new goal that is emerging in MS treatment, especially for patients with relapsing disease. It is a composite of assessments of disability and MRI. Besides long-term disease activity, the extension study will provide further information regarding the long-term safety of cladribine tablets in highly-active RMS patients.

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4.3 Justification for Dose

Not applicable.

4.4 End of Study Definition

A participant has completed the study if he/she has completed all study parts, including the last study visit and the last scheduled procedure presented in the Schedule of Activities (Section 1.3). After the study completion, the participants' care will continue according to routine clinical practice.

The end of the study is defined as the date of the last participant's last visit, globally.

5 Study Population

The criteria in Sections 5.1 and 5.2 are designed to enroll only participants, who are appropriate for the study; thereby, ensuring the study fulfills its objectives. All relevant medical and nonmedical conditions are considered when deciding whether a participant is suitable for this study.

Prospective approval of protocol deviations to inclusion and exclusion criteria, also known as protocol waivers or exemptions, is not permitted.

Before performing any study assessments that are not part of the participant's routine medical care, the Investigator will confirm that the participant or the participant's legal representative has provided written informed consent, as indicated in Appendix 2.

5.1 Inclusion Criteria

Participants are eligible to be included in the study only if all the following criteria apply:

1. Participants of the MAGNIFY MS trial who received at least a single dose of cladribine tablets during the MAGNIFY MS trial and data on MRI is available/acquired from at least parent study Month 18 or Month 24 visit and EDSS and relapse from parent study Month 24 visit.

Informed Consent

2. Capable of giving signed informed consent, as indicated in Appendix 2, which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and this protocol.

5.2 Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Participant is considered by the Investigator, for any reason, to be an unsuitable candidate for the study.

Prior/Concurrent Clinical Study Experience

2. Participation in other studies/trials.

5.3 Lifestyle Considerations

Not applicable.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened.

6 Study Intervention(s)

Not applicable.

6.1 Study Intervention(s) Administration

Not applicable.

6.2 Study Intervention(s) Preparation, Handling, Storage, and Accountability

Not applicable.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

Not applicable.

6.4 Study Intervention Compliance

Not applicable.

6.5 Concomitant Therapy

Record in the case report form (CRF) all concomitant therapies (e.g., medicines or nondrug interventions) used from the time the participant signs the informed consent until completion of the study, including any changes. For prescription and over-the-counter medicines, vaccines, vitamins, and herbal supplements, record the name, reason for use, dates administered, and dosing information. In addition, the following concomitant therapies will be recorded in the CRF as well:

- Concomitant therapies that are linked to a SAE, which were initiated during the parent study, and are ongoing at the time of enrolling (i.e., signing the informed consent) for the extension study
- Concomitant therapies that were initiated during the potential gap period between the parent study last visit and enrollment (i.e., signing the informed consent) in the extension study

Contact the Medical Monitor for any questions on concomitant or prior therapy.

The protocol does not provide any restrictions regarding the therapies that a patient can be on during the extension study period. Decisions regarding concomitant therapies are at the Investigator's discretion.

- Disease-related: All concomitant medications used for conditions/symptoms related to MS (for example, pain, fatigue or weakness, incoordination, bladder dysfunction, spasticity). In addition, participants who switch to any other DMD, appropriate safety and contraception measures will be followed as per the new DMD's SmPC and local clinical practice.
- Medical history related: All concomitant medications used for a medical condition already reported in the participant's medical history (for instance, any form of pain, especially low back pain, headache, and depression) or family history (primary headache, insomnia, etc.).
- Self-medication: As this is an outpatient study, special care will be taken to question participants on any self-medication, and they will be asked to respond about the details of the administration of the doses and the concomitant medications in a diary. The use of any herbal or natural products, or other "home remedies" is allowed. However, the use of these products, and the use of vitamins, nutritional supplements and all other concomitant medicinal products should also be noted in a diary.
- Relapse management: In case of neurological events related to MS, with relapse criteria (Section 8.1.3.1), treatment will be at the discretion of the Investigator, following local good medical practice and international guidelines.

6.6 Dose Selection and Modification

Not applicable.

6.7 Study Intervention after the End of the Study

Not applicable.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Not applicable.

7.2 Participant Discontinuation/Withdrawal from the Study

- A participant may withdraw from the study at any time, at his/her own request or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons.
- A participant will be withdrawn from the study if the participant enrolls in another study.
- At the time of discontinuing from the study, if possible, a discontinuation visit will be conducted, as listed in the Schedule of Activities (Section 1.3). The Schedule of Activities specifies the data to collect at study discontinuation and follow-up, and any additional evaluations that need to be completed. If a physical visit is not possible, a telephone call option is provided, to obtain a reason for discontinuation and the safety assessment.
- If the participant withdraws consent for future involvement in the study, any data collected up to that point may still be used, but no future data can be generated, and any biological samples collected will be destroyed, unless the Investigator obtains permission to retain and further evaluate the samples.
- A participant has the right at any time to request destruction of any biological samples taken. The investigator will document this in the site study records.
- Participants who are discontinued/withdrawn from the study will not be replaced.
- The Investigator will secure the safety of the study participants and make every attempt to collect data.

7.3 Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions will be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wants to or should continue in the study.
- Before a participant is deemed “lost to follow-up”, the Investigator or designee will make every effort to regain contact with the participant: 1) where possible, make 3 telephone calls; 2) if necessary, send a certified letter (or an equivalent local method) to the participant’s last known mailing address, and 3) if a participant has given the appropriate consent, contact the participant’s general practitioner for information. These contact attempts will be documented in the participant’s medical record.

- If the participant continues to be unreachable, he/she will be deemed as "lost to follow-up".

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in the Schedule of Activities (Section 1.3).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns are discussed with the Sponsor immediately upon occurrence or awareness.
- Adherence to the study design requirements, including those specified in the Schedule of Activities, is essential and required for study conduct.
- All screening evaluations will be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened, to confirm eligibility, and if applicable, record reasons for screening failure.
- Prior to performing any study assessments that are not part of the participant's routine medical care, the Investigator will obtain written informed consent as specified in Appendix 2.
- Procedures conducted as part of the participant's routine medical care (e.g., blood count) and obtained before signing of the ICF may be used for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the Schedule of Activities.
- Once the participant has provided informed consent for the extension study, they will be assigned a Participant ID Number (the same as or linked to the Participant ID Number used in the parent study).
- Among data obtained from the parent study are baseline information including demography, medical history, concomitant medications, and disease (MS) status and history.
- The results of the assessments and procedures will be stored in the extension study electronic data capture (EDC). Further details regarding the data collection are provided in Appendix 2 and the eCRF Completion Instructions.
- 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. They 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 Sponsor or its designated organization contain no mention of any participants' names.
- This extension study will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform visits to the study site at regular intervals. Further information regarding monitoring is provided in the Study Monitoring Plan.
- A maximum of 25 mL of blood will be collected in any one-month period from each participant in the study, including any extra assessments that may be required (Appendix 9).

CCI [redacted]

Baseline visit

The extension Baseline is planned to coincide with the parent study last visit (Month 24 Visit of MAGNIFY MS trial). For participants who complete the parent study before the recruitment is open for the extension study enrollment, the Baseline visit will be planned later (after the parent study last visit and before Visit 1). The following procedures will be performed at extension Baseline:

- Informed consent and inclusion/exclusion criteria
- Collection of demography and medical history (see Section 8.3.1)
- Blood sample for CCI [redacted] testing (see Section 8.7)
- Blood sample for CCI [redacted] (see Section 8.8)
- In case there is a gap period between the parent study last visit and extension Baseline: Data will be collected retrospectively for any EDSS (if done), relapses, AEs/SAEs (as described in Section 8.3.1), and concomitant medications that may have been performed/initiated in that time period.

Visit 1

Visit 1 is planned 12 months (± 30 days) since the parent study last visit. The following procedures and assessments will be performed at the Visit 1:

- Efficacy assessments and procedures: MRI, assessment of disability, assessment of cognitive function, relapse reporting
- Safety assessment: AEs, physical examination, vital signs
- Collection and review of patient diary

CCI [redacted]

CCI [redacted]

CCI [redacted]

- Reporting of concomitant medications and procedures

Visit 2

Visit 2 is planned 24 months (± 30 days) since the parent study last visit. The following procedures and assessments will be performed at the Visit 2:

- Efficacy assessments and procedures: MRI, assessment of disability, assessment of cognitive function, relapse reporting

- Safety assessment: AEs, physical examination, vital signs
- Collection and review of patient diary
- CCI [redacted]
- Reporting of concomitant medications and procedures

8.1 Efficacy Assessments and Procedures

A schedule of the tests and evaluations to be conducted during this extension study is located in Section 1.3.

Attempts should be made to conduct study visits on the same day as the neurological exam and/or MRI, and/or blood sample collection. However, when this is not possible, a window of ± 5 days will be allowed.

Assessments related to EDSS/CCI [redacted] should be done by the Investigator. It is not needed to have a separate rater for neurological assessments.

Training modules are recommended for the sites about the assessments for sake of low interrater variability. Whenever possible, the same assessor should manage the same patient for these scales.

8.1.1 Magnetic Resonance Imaging

All scans will be performed according to a standard protocol detailed in a separate MRI scan user's manual.

8.1.1.1 MRI Scanning Procedure

The MRI measures of white matter lesional activity (i.e. new/enlarging T2 lesions or Gd+ T1 lesions) and those of brain atrophy (i.e. the percentage of brain volume change) have shown to be valid surrogate endpoints for clinical outcomes. CCI [redacted]

CCI [redacted]

- [redacted]
- [redacted]
- [redacted]

Restrictions for the MRI schedule:

In order to prevent interferences caused by a DMD, steroid or adrenocorticotropic hormone (ACTH) administration or by relapse, the following restrictions will apply:

- For any relapse that may require a steroid or ACTH treatment, the MRI acquisition should be planned as scheduled and at least occurring after 30 days of the last dose of steroid/ACTH.

- For any relapse that may require a DMD treatment, if the scheduled MRI is in the next 30 days, acquire MRI in advance before initiation of DMD. If DMD already initiated without possibility to acquire MRI in advance, discuss each case with a Medical Monitor on how to handle the MRI acquisition.

All scans will be performed according to a standard protocol detailed in a separate Image Acquisition Guidelines document. Central imaging core lab will independently perform the analysis of all MRI scans to meet study endpoints. As with other laboratory tests and clinical measures, strict adherence to the MRI scanning protocol, and prompt handling of the scans is essential in obtaining a meaningful result.

Investigator should also ensure that the MRI scan is locally evaluated either by themselves/site radiologist for safety to rule out progressive multifocal leukoencephalopathy and/or any serious central nervous system disease (e.g., tumor, stroke etc.). For participants switching to other DMDs the safety/follow-up will be additionally assessed by the Investigator. Any unscheduled MRI acquired for such switching or for other safety reasons during the study will be analyzed by the Investigator/site radiologist as per standard of care.

Prior to participant assessment, each study site may be asked to send a ‘test’ or ‘dummy-run’ scan to assess image quality and shipment procedures, to evaluate the accessibility of the electronic data carrier, and to assess the ability to correctly reposition participants so as to get comparable brain images. Only upon final approval of this test scan, sites will be allowed to begin assessing participants.

Each participant should be scanned using the same machine throughout the study. In case of machine change, or hardware/software upgrade the necessity to complete another test scan using the new equipment should be agreed upon with the central imaging core lab.

8.1.2 Disability Assessments

8.1.2.1 Expanded Disability Status Scale/ CCI [redacted]

CCI [redacted]

The EDSS is a neurological assessment to evaluate disability in neurologic deficient patients with MS. It will be completed by the evaluating physician, who evaluates the participant's state according to the KFS Grades. The repeated application allows the measurement of the level of disability over time (Kurtzke 1983).

An EDSS progression is defined as an increase in the EDSS scale as follows:

- If the Baseline* EDSS score is 0, the increase must be ≥ 1.5 units
- If the Baseline* EDSS score is ≥ 0.5 or ≤ 4.5, the increase must be ≥ 1.0 units
- If the Baseline* EDSS score ≥ 5.0 the increase must be ≥ 0.5 units

Sustained EDSS progression is defined as EDSS progression (as defined above) confirmed by subsequent measurements of at least 3 months apart.

*The extension study-specific starting point for analyses is the parent study baseline (before the initial dose of cladribine tablets).

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[redacted]

8.1.3 Relapses

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

8.1.3.1 Relapse Evaluation

All the following criteria should be met for establishing a (qualifying) MS clinical relapse:

1. Neurological abnormality, either newly appearing or re-appearing, with abnormality specified by both
    a. Neurological abnormality separated by at least 30 days from onset of a preceding clinical event, and
    b. Neurological abnormality lasting for at least 24 hours
2. Absence of fever or known infection (fever with temperature [axillary, orally or intra auricular] > 37.5°C / 99.5 °F)
3. Objective neurological impairment, correlating with the participant's reported symptoms, defined as either:
    a. Increase in at least one of the functional system scores of the EDSS, or
    b. Increase of the total EDSS score

The occurrence of paresthesia, fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not be classified as an MS clinical relapse.

8.1.3.2 Procedure for Relapse Evaluation

The participant will be instructed to immediately contact the treating physician if he/she develops new or re-occurring or worsening neurological (including visual) symptoms. At each scheduled visit, the participant will be asked whether any such symptoms have occurred.

Upon reporting symptoms indicative of a relapse, the Investigator will assess whether the symptoms occurred in the presence of fever or infection (in case of an unscheduled phone-contact, the treating physician may simply ask the participant). If fever or infection is excluded, the Investigator must arrange for a neurological examination as soon as possible, at the latest within 7 days following the reporting of the event. If fever or infection cannot be excluded, the neurological examination by the Investigator will have to be postponed until the fever or the infection have ceased (provided, that the symptoms indicative of relapse are still present).

Based on the respective EDSS scores, in conjunction with the results from previous examinations, the Investigator will assess whether the EDSS criterion for relapse during the course of the study is fulfilled.

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[redacted]

8.1.4 Confirmed Disability Progression

The occurrence of a confirmed disability progression (CDP) is derived from the EDSS score in the analysis phase. The CDP is defined as:

- Yes: sustained increase in EDSS score
- No: no sustained EDSS progression
- Unknown: Otherwise

8.1.5 No Evidence of Disease Activity

No evidence of disease activity (NEDA), also referred to as freedom from disease activity, is a new goal that is emerging in MS treatment. The NEDA-3 is a composite measure including 3 parameters: relapses, cognition and disability progression, and MRI activity, and is derived in the analysis phase. NEDA-3 is defined as the absence of the following 3 conditions:

- Qualifying Relapses (as defined in Section 8.1.3)
- CDP (as defined in Section 8.1.4)
- MRI activity (new/enlarging T2 lesions and/or T1 Gd+ lesions; see Section 8.1)

during the defined period.

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[redacted]

CCI [redacted]

[redacted]

[redacted]

8.1.8 Patient Diary

At the Baseline Visit, participants will be provided with a diary to record details on AEs, and concomitant medications and procedures (Appendix 6). The participant will receive instructions regarding the filling out of the diary.

The patient diary entries must be reviewed by the study coordinator(s)/nurse(s) with the participant to clarify any discrepancies and ensure proper completion. This review must be completed at each visit and the review recorded in the participant's clinic visit notes. The appointed designee will enter in the eCRF (on the correct form, i.e., the AE or concomitant medications and procedures form) what each participant records on his/her form and any information that is obtained after subsequent questioning of the participants.

8.1.9 Data Retrieved from Parent Study

Data from the parent study will be retrieved in the analysis phase, including previous measurements of efficacy assessments, demographic characteristics, and medical history obtained as part of the parent study.

8.2 Safety Assessments and Procedures

The safety profile of cladribine tablets (concerning long-term effects) will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, vital signs, and laboratory tests. At each study visit (Section 1.3), the participant will be queried on changes in his or her disease condition. Comprehensive assessment of any potential toxicity experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AEs, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1. All AEs and SAEs must be reported on the appropriate eCRF page as described in Appendix 7.

The incidence of AEs will be summarized overall, by severity, and by relationship to cladribine tablets. The summary tables will include incidence rates of AEs for overall system organ classes and by preferred term within each system organ class.

More information can be found in Appendix 7 and in the CRF Completion and Monitoring Conventions provided by the Sponsor.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal, and Neurological systems.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Abnormal results will be documented in the CRF.
- Investigators will pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Vital signs will be measured in a semi-supine position after 5 minutes rest and will include body temperature, systolic and diastolic blood pressure, and pulse.

8.3 Adverse Events and Serious Adverse Events

In this section, "study intervention" refers to cladribine tablets (i.e., the study intervention of the MAGNIFY MS parent trial) since no study intervention is administered in this study.

- The definitions of an AE and a SAE are in Appendix 7.
- The Investigator and any qualified designees (e.g., Sub-Investigators) are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE. The Investigator remains responsible for following up AEs that are serious or that caused the participant to discontinue the study, as specified in Section 8.3.3.
- Requests for follow-up will usually be made via the Study Monitor, although in exceptional circumstances the global patient safety department may contact the Investigator directly to obtain further information or to discuss the event.

8.3.1 Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information

- All SAEs will be collected from the signing of the ICF until the last study visit at the time points specified in the Schedule of Activities (Section 1.3). Beyond this reporting period, any new unsolicited SAEs that the Investigator spontaneously reports to the Sponsor will be collected and processed.
- All AEs will be collected from the signing of the ICF until the last study visit at the time points specified in the Schedule of Activities.

- The date of the last procedure according to the parent study protocol (i.e., the parent study exit date) and the date of signing informed consent for the extension study (i.e., the extension study enrollment date) is important to determine how AEs/SAEs should be recorded and reported:
  - Ongoing SAEs and events of lymphopenia (also if not serious) with an onset date prior to the parent study exit date will be recorded on the Medical History/Current Medical Conditions CRF. If the condition worsens, a new SAE will be recorded on the AE CRF page and reported as specified in Appendix 7. Other non-serious AEs which are ongoing at the parent study exit date will not be recorded in the extension study.
  - AEs/SAEs with an onset date after the parent study exit date and before the extension study enrollment date will be collected retrospectively (after obtaining informed consent) and recorded on the AE CRF page for the extension study.
  - AEs/SAEs with an onset date after the extension study enrollment date will be recorded on the AE CRF page for the extension study.
- All SAEs will be recorded and reported to the Sponsor or designee immediately and under no circumstance will this exceed 24 hours, as indicated in Appendix 7. The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available using the same procedure that was used for the initial report.
- Investigators are not obligated to actively solicit AEs or SAEs after the end of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

8.3.2 Method of Detecting Adverse Events and Serious Adverse Events

At each study visit, the participant will be queried on changes in his or her condition. In addition, the participants will be asked to record AEs in a continuous manner in their patient diary.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and non-leading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with cladribine tablets, any other potential causal factors, any treatment given or other action taken, and its outcome. In addition, serious cases should be identified, and the appropriate seriousness criteria documented.

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are in Appendix 7.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

After the initial AE/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Reasonable attempts to obtain this information will be made and documented. It is also the Investigator's responsibility to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is in Appendix 7.

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

Prompt notification by the Investigator to the Sponsor of an SAE (particularly life-threatening and deaths) is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.

Individual Case Safety Reports will be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators, as necessary.

An Investigator who receives an Individual Case Safety Report describing a SUSAR or other specific safety information (e.g., Emerging Safety Issue Report, summary or listing of SAEs/SUSARs) from the Sponsor will review and then file it along with the SmPC in the Investigator's Site File and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants will be collected from the signing of the ICF until the last study visit at the time points specified in the Schedule of Activities (Section 1.3).
- If a pregnancy is reported, the Investigator will inform the Sponsor within 24 hours of learning of the pregnancy and will follow the procedures specified below for collection of pregnancy information.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Collection of Pregnancy Information

Pregnancy relevant information on male participants with female partners will not be collected due to lapse of more than 6 months since the last dose of cladribine tablets.

Female Participants who become pregnant

- The Investigator will collect pregnancy information on any female participant who becomes pregnant while she is in the study. The initial information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of the pregnancy.
- The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate, and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be reported as an AE or SAE and recorded in the eCRF.
- A spontaneous abortion (occurring at <22 weeks gestational age) or stillbirth (occurring at >22 weeks gestational age) is always considered to be an SAE and will be reported as such.
- Any post-study pregnancy related SAE considered reasonably related to cladribine tablets by the Investigator will be reported to the Sponsor as specified in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study may continue in the study, as no study intervention is involved, and the assessments are largely part of routine medical care for MS.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

The following disease-related events are common in participants with highly-active RMS and can be serious/life threatening:

- Symptoms and signs of relapse or worsening of MS

Because these events are typically associated with the disease under study, they will not be reported according to the standard process for expedited reporting of AEs and SAEs even though the event may meet the definition of an AE or SAE. These events will be recorded on the relapse module of the eCRF page within 15 days after the visit.

However, if either of the following conditions applies, then the event will be recorded and reported as an SAE (instead of a disease-related event):

- The event is, in the Investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant (i.e. worsening not consistent with the anticipated natural progression of the disease).

  OR

- The Investigator considers that there is a reasonable possibility that the event was related to study intervention.

8.4 Treatment of Overdose

Not applicable.

8.5 Pharmacokinetics

Not applicable.

8.6 Pharmacodynamics

Not applicable.

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- [redacted]
- [redacted]
- [redacted]
- [redacted]

CCI [redacted]

- [redacted]
- [redacted]

[redacted]

8.9 Immunogenicity Assessments

Not applicable.

[redacted]

9.1 Statistical Hypotheses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory.

[redacted]

CCI [redacted]

[redacted]	[redacted]		[redacted]	
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

9.3 Populations for Analyses

The analysis population are specified in Table 5. The final decision to exclude participants from any analysis population will be made prior to database lock.

Table 5: Analysis Populations

Analysis Set	Description
Enrolled Set	All participants who provided informed consent.
Full Analysis Set (FAS)	The FAS will include all enrolled, eligible participants.
Per protocol set	All participants from the FAS who fulfil the highly-active relapsing MS inclusion criteria (i.e., all subjects from the FAS without a protocol deviation for the highly-active relapsing MS inclusion criteria).
Safety Analysis Population (SAF)	All participants treated with at least one dose of cladribine tablets during the parent study.
Treatment Completer Set	All participants from the FAS who completed the full treatment course of the first and second year in the parent study.

FAS: Full Analysis Set; MS: Multiple Sclerosis; SAF: Safety Analysis Population.

Further analysis sets and subgroups for analysis may be defined in the IAP.

9.4 Statistical Analyses

Participants' characteristics will be summarized with the following measures: mean with standard deviation, minimum and maximum for normally distributed continuous variables, median with interquartile range, minimum and maximum for other continuous variables and counts with percentages for categorical variables.

The study dataset comprises of multiple outcome assessments made for each participant over a 4-year period (2 years of the parent and 2 years of the extension study). Therefore, due to the longitudinal nature of the data and the lengthy follow-up period, it is likely that missing outcome data will be present due to loss to follow-up. Patterns and degrees of missingness will be summarized and will inform the approach taken to dealing with missing data.

9.4.1 Efficacy Analyses

All efficacy analyses will be performed on the Full Analysis Set (FAS) population (Table 6). In addition, the primary and secondary analyses may be repeated for other analysis populations, as described in the IAP.

Table 6: Analysis of Efficacy Endpoints

Endpoint	Statistical Analysis Methods
Primary	• Proportion of participants with NEDA-3 during 2 years of the extension study. NEDA-3 will be analyzed with a Kaplan-Meier (KM) time-to-event method to reduce the impact of unknown/missing information (assuming missing at random [MAR]). • The 95% confidence intervals (CIs) for KM estimate at the end of the 2 years period will be provided. • Statistical methods to handle any deviations from MAR will be detailed in SAP.
Secondary	• For the secondary analyses, the methods will be similar as for the primary analysis.
CCI [redacted]	[redacted]

CI: Confidence Interval; KM: Kaplan-Meier; MAR: Missing At Random; NEDA-3: Three Parameter No Evidence of Disease Activity; SAP: Statistical Analysis Plan.

9.4.2 Safety Analyses

All safety analyses will be performed on the Safety Analysis population. Information on AEs and SAEs will be presented by System Organ Class and Preferred Term within each system organ class according to MedDRA (Table 7).

Table 7: Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable.
Secondary	AEs and SAEs will be collected and summarized by System Organ Class and Preferred Term within each system organ class according to MedDRA, providing detail of the frequency, type, severity, and other outcome of the events. Further exploratory analyses may be specified in the Integrated Analysis Plan finalized before database lock.
CCI [redacted]	[redacted]

MedDRA: Medical Dictionary for Regulatory Activities; SAE: Serious adverse event; AE: adverse event

9.4.3 Other Analyses

The study population enrolled in the extension study will be compared to the study population initially enrolled in the parent study based on summary statistics of the baseline characteristics.

9.4.4 Sequence of Analyses

Final analyses will be performed at the end of study or after Visit 1 (at the end of Year 3 after the initial dose of cladribine tablets). In addition, interim analysis at extension study Baseline or at the end of Year 3 after the initial dose of cladribine tablets may be performed (further details on interim analyses will be provided in the IAP).

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CCI [redacted]

11 Appendices

Appendix 1 Abbreviations

CCI [redacted]	[redacted]
ACTH	Adrenocorticotropic hormone
AE	Adverse event
CCI [redacted]	[redacted]
CDP	Confirmed disability progression
CRF	Case report form
CRO	Contract Research Organization
CCI [redacted]	[redacted]
CSR	Clinical study report
CCI [redacted]	[redacted]
DMD	Disease modifying drug
eCRF	Electronic Case report form
EDC	Electronic data capture
EDSS	Expanded Disability Status Scale
CCI [redacted]	[redacted]
FAS	Full analysis set
GCP	Good Clinical Practice
IAP	Integrated Analysis Plan
ICF	Informed consent form
ICH	International Council for Harmonization
IEC	Independent Ethics Committee
CCI [redacted]	[redacted]
[redacted]	[redacted]
ISMP	Integrated Study Management Plan
CCI [redacted]	[redacted]
KM	Kaplan-Meier
LLPP	Low dose/placebo
MAR	Missing at random
MedDRA	Medical Dictionary for Regulatory Activities

MRI	Magnetic resonance imaging
MS	Multiple Sclerosis
MTI	Magnetization transfer imaging
CCI	[redacted]
NEDA	No Evidence of Disease Activity
NEDA-3	Three parameter No Evidence of Disease Activity
CCI	[redacted]
[redacted]	[redacted]
CCI	[redacted]
CCI	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
PRO	Patient reported outcome
RMS	Relapsing Multiple Sclerosis
CCI	[redacted]
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious adverse event
SAF	Safety analysis population
SC	Steering Committee
CCI	[redacted]
SmPC	Summary of Product Characteristics
CCI	[redacted]
SUSAR	Suspected unexpected serious adverse reactions
CCI	[redacted]
CCI	[redacted]

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with enough, accurate financial information, as requested, for the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. This information is required during the study and for 1 year after completion of the study.

Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the participant or his/her legally authorized representative and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally authorized representative will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; International Council for Harmonisation (ICH) guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the Institutional Review Board (IRB)/Independent Ethics. Committee (IEC) or study center.
- The medical record will include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent will also sign the ICF.
- If the ICF is updated during their participation in the study, participants will be re-consented to the most current, approved version.
- A copy of the ICF(s) will be provided to the participant or the participant's legally authorized representative.
- The original signed and dated consent will remain at the Investigator's site and will be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

Data Protection

- The Sponsor will assign a unique identifier to participants after obtaining their informed consent. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any identifiable information will not be transferred.
- The Sponsor will inform participants that their personal study-related data will be used per local data protection and privacy laws. The level of disclosure will also be explained to the participant and pregnant partners (if applicable), who will be required to give consent for their data to be used, as specified in the informed consent.
- The participants will be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other Sponsor-appointed, authorized personnel, by appropriate IRB/IEC members, and by regulatory authority inspectors. All such persons will strictly maintain participants' confidentiality.

Study Administrative

Sponsor

- The Sponsor of this extension study is Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.
- Sites, that participated in the parent study (MAGNIFY MS trial), from Europe (including the following countries: Austria, Czech Republic, Finland, France, Germany, Hungary, Italy, Spain, Sweden, and the United Kingdom), Australia, Canada, and Israel will be approached for participation in this study. About 80 sites are expected to participate.
- The Coordinating Investigator listed on the title page represents all Investigators for decisions and discussions on this study, per ICH GCP. The Coordinating Investigator will provide expert medical input and advice on the study design and execution and is responsible for the review and signoff of the clinical study report (CSR).

  The study will appear in the following clinical studies registries: EU Clinical Trials Register, ClinicalTrials.gov, and national registries as per local regulations.

Scientific Steering Committee

- A Steering Committee (SC) will be established to ensure that the study meets scientific standards. The SC Charter will be in the place that describes the SC responsibilities. The SC is a multidisciplinary group of lead study Investigators, medical experts, and Sponsor's personnel, who, collectively, have the scientific, medical, and clinical study management experience to design, conduct and evaluate the study. The SC provides advice and recommendations with regard to the design, the conduct, and the evaluation of the study. The SC is responsible for safeguarding the interests of participating participants and for the conduct of the study.

Contract research organization

- A contract research organization (CRO), IQVIA, will undertake the operational aspects of this study with oversight by the Sponsor. Details of such structures and associated procedures will be defined in a separate Integrated Study Management Plan (ISMP).
- The ISMP will be prepared by the CRO. Clinical quality assurance will be performed under the responsibility of the Development Quality Assurance department at Merck KGaA.

Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and the following:
  - Consensus ethical principles derived from international guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations

- The Investigator will submit the protocol, protocol amendments (if applicable), ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC will review and approve them before the study is initiated.
- Any protocol amendments (i.e., changes to the protocol) will be documented in writing and require IRB/IEC approval before implementation of changes, except for changes necessary to eliminate an immediate hazard to study participants. When applicable, amendments will be submitted to the appropriate Health Authorities.
- The Investigator will be responsible for the following:
    - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently per the IRB's/IEC's requirements, policies, and procedures
    - Notifying the IRB/IEC of serious adverse events (SAEs) or other significant safety findings, as required by IRB/IEC procedures
    - Providing oversight of the study conduct at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations
- The protocol and any applicable documentation will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

Clinical Study Insurance and Compensation to Participants

- Insurance coverage will be provided for each country participating in the study. Insurance conditions will meet good local standards, as applicable.

Clinical Study Report

- After study completion, the Sponsor will write a CSR in consultation with the Coordinating Investigator, Principal Investigator (for single center studies), and any SC or other relevant study-appointed committees or groups.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support the publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by agreement.
- Authorship will be determined by agreement and in line with International Committee of Medical Journal Editors authorship requirements.

Dissemination of Clinical Study Data

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

- Disclosure of CSRs, periodic safety reports, and clinical study summary reports is only required, if applicable by local law and regulations.
- Posting of data on the European Clinical Trials Register and ClinicalTrials.gov is planned and will occur 12 months after the last clinic visit of the final study participant or another appropriate date to meet applicable requirements.

Data Quality Assurance

- All participant study data will be recorded on printed or electronic case report forms (CRFs) or transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are complete, accurate, legible, and timely by physically or electronically signing the CRF. Details for managing CRFs are in the Data Management Plan and Data Validation Plan.
- For patient reported outcome (PRO) data (e.g., quality of life and pain assessments), ePRO will be used.
- The Investigator will maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator will permit study-related monitoring, quality assurance audits, IRB/IEC review, and regulatory agency inspections and provide direct access to the study file and source data.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are in the Monitoring Plan or contracts.
- The Sponsor or designee is responsible for data management of this study, including quality checking of the data and maintaining a validated database. Database lock will occur once quality control and quality assurance procedures have been completed. Details will be outlined in Data Management documents and procedures.
- Study Monitors will perform ongoing source data verification to confirm that data in the CRF are accurate, complete, and verifiable; that the safety and rights of participants are being protected; and that the study is being conducted per the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- The Investigator will retain records and documents, including signed ICFs, pertaining to the conduct of this study for 15 years after study completion, unless local regulations, institutional policies, or the Sponsor requires a longer retention. No records may be destroyed during the retention period without the Sponsor's written approval. No records may be transferred to another location or party without the Sponsor's written notification.

Source Documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected.

- The Investigator will keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file will identify each participant, contain the following demographic and medical information for the participant, and will be as complete as possible:
  - Participant's full name, date of birth, sex, height, and weight
  - Medical history and concomitant diseases
  - Prior and concomitant therapies (including changes during the study)
  - Study identifier (i.e., the Sponsor's study number) and participant's study number
  - Dates of entry into the study (i.e., signature date on the informed consent) and each visit to the site
  - Any medical examinations and clinical findings predefined in the protocol
  - All AEs
  - Date that the participant left the study, including any reason for early withdrawal from the study.
- All source data will be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document will have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical evaluation of these records will be performed, documented, signed and dated by the Investigator.
- Data recorded on printed or electronic CRFs that are transcribed from source documents will be consistent with the source documents or the discrepancies will be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records will be available.
- The Study Monitors will use printouts of electronic files for source data verification. These printouts will be signed and dated by the Investigator and kept in the study file.
- Source documents are stored at the site for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. The Investigator ensures that no destruction of medical records is performed without the Sponsor's written approval.
- Definition of what constitutes source data is found in the ISMP.

Study and Site Start and Closure

First Act of Recruitment

- The study start date is the date when the clinical study will be open for recruitment.
- The first act of recruitment is when the first site is opened and will be the study start date.

Study Closure and Site Termination

- The Sponsor reserves the right to close the study site or terminate the study at any time and for any reason. Study sites will be closed upon study completion. A study site is considered

closed when all required documents and study supplies have been collected and a site closure visit has been completed.

- The Investigator may initiate site closure at any time, provided there is reasonable cause and enough notice is given in advance of the intended termination.
- Reasons for the early closure of a study site by the Sponsor or Investigator may include:
    - Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
    - Inadequate recruitment of participants by the Investigator
    - Discontinuation of further development of the Sponsor’s compound
- If the study is prematurely terminated or suspended, the Sponsor will promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator will promptly inform the participants and assure appropriate participant therapy and/or follow-up.

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Required Blood Volume

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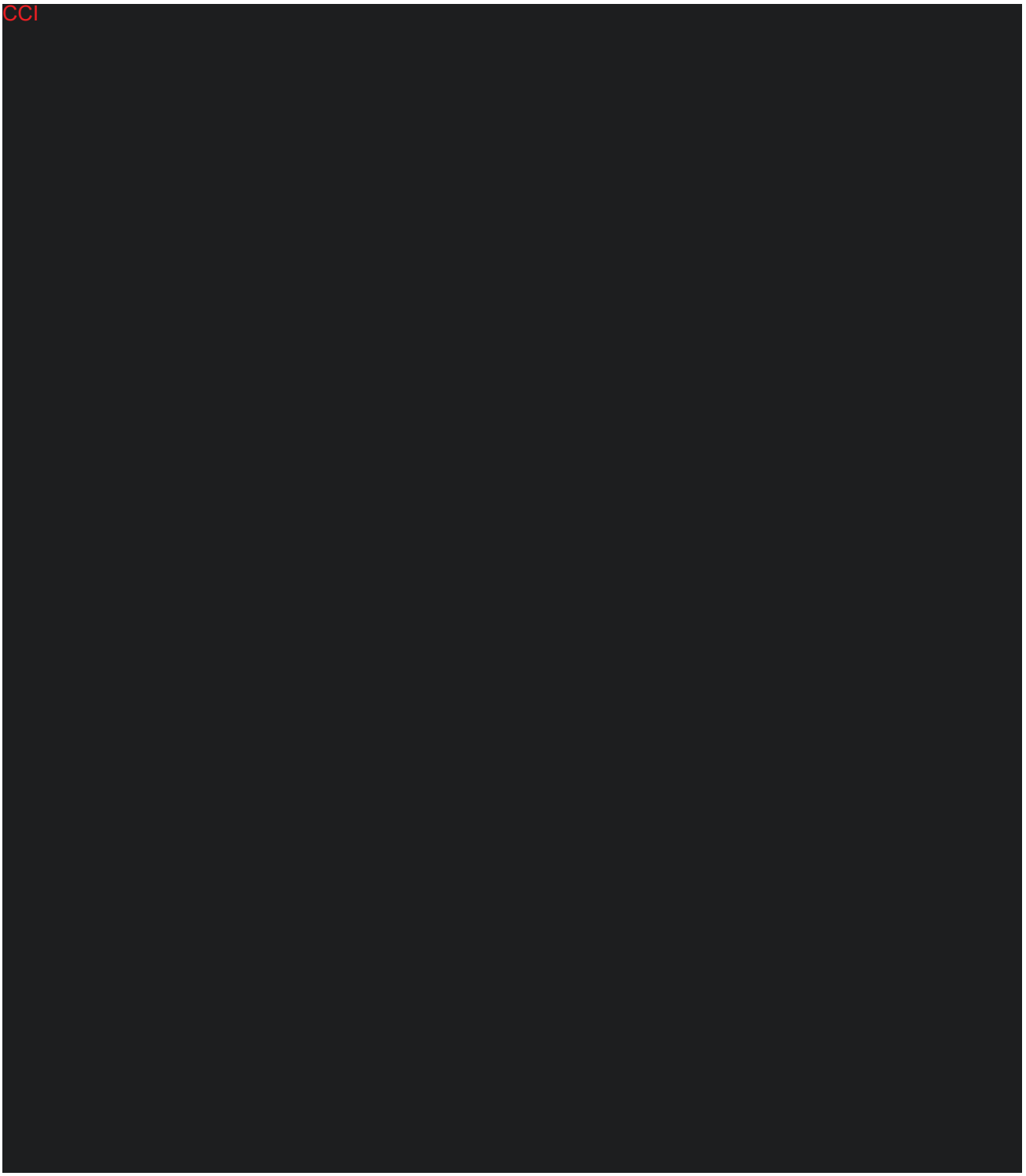

Appendix 6 Example of Patient Diary

Patient Diary Card: Month ___ to ____	
Patient initials:	Patient number:

Dear participant,

Please complete this diary card (with a pen) between study visits and always take it with you to the hospital when you visit.

This diary has been designed to help us follow your general health and any problem or discomfort you may experience between the study visits and to record all medication you take.

Medication record			
Start Date	Stop Date	List any new medications for changes in the medications	Specify reason for taking any specific medication. All medications should be listed here, e.g. painkillers, …, as well.

Symptom record		
Start Date	Stop Date	Briefly list any problem or discomfort you experienced (use as many lines as necessary)

Appendix 7 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

In this section, "study intervention" refers to cladribine tablets (i.e., the study intervention of the MAGNIFY MS parent study) since no study intervention is administered in this study.

AE Definition

AE Definition
• An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether considered related to the study intervention or not. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention. For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.
Events <u>Meeting</u> the AE Definition
• Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. However, as the study intervention (cladribine tablets) was administered during the parent study, only new conditions not detected/diagnosed during the parent study need to be collected. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or a SAE. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as an AE or a SAE if they fulfill the definition of an AE or SAE.
Events <u>NOT</u> Meeting the AE Definition
• Unless judged by the Investigator to be more severe than expected for the participant's condition, any clinically significant abnormal laboratory findings, other abnormal safety assessments that are associated with the underlying disease, the disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) will not be reported as AEs/SAEs, unless the participant's general condition is more severe than expected for the his/her condition and/or unless the outcome is fatal within the AE reporting period, as defined in Section 8.3.1.

Symptoms and signs of relapse or worsening of MS since the previous visit will usually be captured in the context of the efficacy assessment, and recorded on the relapse module of the eCRF. Therefore, symptoms, relapses or worsening of MS will not be considered as AEs unless considered possibly or probably related to cladribine tablets (i.e. worsening is not consistent with the anticipated natural progression of the disease).

SAE Definition

If an event is not an AE per the definition above, then it cannot be an SAE even if serious conditions are met (e.g., hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

a. Results in death

b. Is life-threatening

The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

- In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE will be considered serious.

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is **not** considered an AE.
- However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (i.e., undesirable effects of any administered treatment) must be documented and reported as SAEs.

d. Results in persistent disability/incapacity

The term disability means a substantial disruption of a person's ability to conduct normal life functions.

This definition is **not** intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment will be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events are usually considered as serious.
- Examples of such events include invasive or malignant cancers, 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 drug dependency or drug abuse.

Any suspected transmission of an infectious agent via a diagnostic procedure is also considered an SAE for reporting purposes, as specified below for reporting SAEs.

Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- As needed, the Sponsor may ask for copies of certain medical records (e.g., autopsy reports, supplemental lab reports, documents on medical history/concomitant medications, discharge letters), as supporting source documentation. All participant identifiers, except the participant number, will be redacted on these copies before submission to the Sponsor.

- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.
- Specific guidance is in the CRF Completion and Monitoring Conventions.

Assessment of Intensity

The Investigator will assess the intensity of each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. Do not confuse an AE that is assessed as severe with a SAE. Severe is a category used to rate the intensity of an event; both AEs and SAEs can be assessed as severe.

  An event is defined as "serious" when it meets at least 1 of the predefined criteria specified in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The Investigator will assess the relationship between study intervention and each AE/SAE occurrence:
  - Unrelated: Not reasonably related to study intervention. AE could not medically (pharmacologically/clinically) be attributed to study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to study intervention. AE could medically (pharmacologically/clinically) be attributed to study intervention.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The Investigator will also consult the Investigator Brochure and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator will document in the medical notes that he/she has reviewed the AE/SAE and assessed causality.
- There may be situations when an SAE has occurred, and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. To meet the reporting timeline, the causality assessment is not required for the initial report.

- The Investigator may change his/her causality assessment after considering follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator will perform or arrange for the conduct of supplemental measurements and/or evaluations, as medically indicated or as requested by the Sponsor to elucidate the nature and/or causality of the AE or SAE, as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor within 24 hours of receipt of the information.

Reporting of SAEs

SAE Reporting by an Electronic Data Collection Tool

- The primary mechanism for reporting an SAE to the Sponsor or its designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool, specified below, to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form or to the Sponsor's safety department.
- By exception, an SAE (or follow-up information) may be reported by telephone. The site will complete the electronic SAE data entry immediately thereafter.

SAE Reporting by a Paper Form

- SAE reporting on a paper report form is used as a back-up method for an EDC system failure. The form includes completion instructions for the Investigator, names, addresses, and telephone and fax numbers. All information from the paper form will be transcribed into the electronic form as soon as the system becomes available.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the form within 24 hours after becoming aware of the event.
- Additional documents (e.g. laboratory reports, autopsy report, hospital discharge letter) and relevant pages from the CRF may be required in addition (e.g. medical history, concomitant medication). The data provided will be consistent with the information in the CRF.

Reporting of Pregnancies

- Pregnancy will be reported whether related to the study intervention using the applicable paper form.
- The applicable form will be used to report if an abnormal outcome of the pregnancy occurs and the child/fetus sustains an event.
- Facsimile transmission (fax to mail) of the paper form or any follow-up information is the preferred method for transmission and will be done within 24 hours to the Sponsor or its designee.

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Appendix 10 Contraception

According to cladribine tablets (Mavenclad®) SmPC, there are no requirements regarding contraception that apply after 6 months since the last dose. At the time of enrollment in the MAGNIFY MS Extension study, participants will have completed treatment. The treatment start was since minimally 2 years, with minimally 12 months since starting the second year treatment.

Appendix 11 Sponsor Signature Page

Appendix 11 Sponsor Signature Page

Study Title:	A 2-year extension study to evaluate long-term effectiveness of Mavenclad® in participants who have completed Trial MS700568_0022 (MAGNIFY MS)
Regulatory Agency Identifying Numbers:	2020-003995-42
Clinical Study Protocol Version:	20 August 2020/Version 1.0

I approve the design of the clinical study:

PPD

Signature

24-Aug-2020

Date of Signature

PPD

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

E-mail address:

Appendix 12 Coordinating Investigator Signature Page

Appendix 12 Coordinating Investigator Signature Page

Study Title:	A 2-year extension study to evaluate long-term effectiveness of Mavenclad® in participants who have completed Trial MS700568_0022 (MAGNIFY MS)
Regulatory Agency Identifying Numbers:	2020-003995-42
Clinical Study Protocol Version:	20 August 2020/Version 1.0
Site Number:	

I approve the design of the clinical study, am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

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

Appendix 13 Principal Investigator Signature Page

Study Title:	A 2-year extension study to evaluate long-term effectiveness of Mavenclad® in participants who have completed Trial MS700568_0022 (MAGNIFY MS)
Regulatory Agency Identifying Numbers:	2020-003995-42
Clinical Study Protocol Version:	20 August 2020/Version 1.0
Site Number:	

I am responsible for the conduct of the study at this site and understand and will conduct it per the clinical study protocol, any approved protocol amendments, International Council on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

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

_____ _____

Signature Date of Signature

Name, academic degree:

Function/Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address: