Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	A 2-year follow-up study to assess cognition and health-related quality of life in participants with highly-active relapsing multiple sclerosis, having participated in the CLARIFY MS trial
Study Number:	MS700568_0158
Protocol Version:	28 June 2021/Version 2.0
Merck [Compound]:	Mavenclad®
Merck Registered Compound Name in Japan:	Not Applicable
Study Phase:	IV
Short Title:	Cognition and HRQoL in adults with highly-active RMS in Year 3 and 4 after initial Mavenclad® dose
Acronym or Abbreviation:	CLARIFY MS Extension
Coordinating Investigator:	Prof. PPD , PPD
Sponsor Name and Legal Registered Address:	**Sponsor**: Merck Healthcare KGaA, Darmstadt, Germany an affiliate of Merck KGaA, Darmstadt, Germany Frankfurter Str. 250, 64293 Darmstadt, Germany **Medical Responsible:** Name: PPD , MD, MSc Phone: PPD
Regulatory Agency Identifying Numbers:	EudraCT: 2020-003874-30
Keywords	Cladribine tablets; patient-reported outcomes; long-term effects

Protocol Amendment Summary of Changes

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	19-Aug-2020
2.0	Global Amendment to the Original Protocol	28-Jun-2021

Protocol Version [2.0] (28-June-2021)

Overall Rationale for the Amendment

Section # and Name	Description of Change	Brief Rationale
Section 1.3. Schedule of Activities; Section 4.2. Scientific Rationale for Study Design; Section 8. Study Assessments and Procedures; Section 8.1.3. COVID-19 Survey; Section 9.4.3. Other Analyses	Addition of a COVID-19 Survey for participants	To collect data on the potential impact of COVID-19 on the study endpoints.
Section 1.3. Schedule of Activities; 8.1. Efficacy Assessments and Procedures; 8.1.5.1. Expanded Disability Status Scale/ CCI CCI	CCI	
Section 8.3.5. Pregnancy	Addition of pregnancy reporting details during the gap period	Details of pregnancy occurring during the gap period need to be collected in the adverse event (AE) page and reported to Global Patient Safety.
CCI		
Throughout	Minor editorial and document formatting revisions	Minor; therefore, have not been summarized.

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1 Protocol Summary

1.1 Synopsis

Protocol Title: A 2-year follow-up study to assess cognition and health-related quality of life in participants with highly-active relapsing multiple sclerosis, having participated in the CLARIFY MS trial

Short Title: Cognition and HRQoL in adults with highly-active RMS in Year 3 and 4 after initial Mavenclad® dose

Rationale: Highly-active relapsing multiple sclerosis (RMS) is characterized by neurological deterioration, causing motor and cognitive dysfunction and impacting health related quality of life (HRQoL). Whilst the randomized control studies on cladribine tablets (Mavenclad®) provide a wealth of information on clinical and safety outcomes, this study will add to the evidence by investigating the long-term effect (over 2 years after initial treatment) on cognition and patient-reported outcomes (PROs) among adults with highly-active RMS.

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

Table 1 Objectives and Endpoints

Objectives	Endpoints
Primary	
To assess cognitive impairment in participants with highly-active relapsing multiple sclerosis (RMS), having participated to the CLARIFY MS trial, at 4 years after initial dose of cladribine tablets	Percentage of participants with no or minimal decline in cognitive function, defined as an improved or stable Symbol Digit Modalities Test (SDMT) score or a decline of 4 points or less in the SDMT score, at 4 years after initial dose of cladribine tablets (M48) compared to SDMT score prior to initial dose of cladribine tablets (CLARIFY MS trial Baseline)
Secondary	
To assess health related quality of life (HRQoL) in participants with highly-active RMS, having participated in the CLARIFY MS trial, at 4 years after initial dose of cladribine tablets	• Change in HRQoL as measured by the Multiple Sclerosis Quality of Life-54 Questionnaire (MSQoL-54) physical and mental health scores at 4 years after initial dose of cladribine tablets (M48) compared to prior to initial dose of cladribine tablets (CLARIFY MS trial Baseline) • Change in HRQoL as measured by MSQoL-54 physical and mental health scores at 4 years after initial dose of cladribine tablets (M48) compared to M24

HRQoL=Health related quality of life; SDMT=Symbol Digit Modalities Test; MSQoL-54=Multiple Sclerosis Quality of Life 54 Questionnaire; RMS=Relapsing Multiple Sclerosis.

Overall Design: This is the extension study to the 2-year CLARIFY MS trial to observe participants during the third and fourth year after the initial cladribine tablet dose; no cladribine tablets will be administered during the extension study period. At the extension study Baseline, data will be collected retrospectively from the potential transition gap period between the CLARIFY MS trial and CLARIFY MS Extension study (i.e., between M24 and extension study Baseline). In addition, participants will attend visits for assessments at the extension study Baseline (planned to coincide with or be as near to M24 as possible to minimize the transition gap period), M36 at 36 months/3 years after initial dose of cladribine tablets, and M48 at 48 months/4 years after initial dose of cladribine tablets.

Disclosure Statement: This will be an open label, single arm, exploratory, multicenter, retrospective and prospective, 2-year Phase IV study. The purpose of the study is the evaluation of the effect of a treatment for highly-active RMS.

Number of Arms: 1

Blinding: Not applicable

Number of Participants: Depending on the drop-out rate of the parent study, it is expected that up to a maximum of 380 participants will be enrolled into the extension study. Assuming a drop-out rate over the course of the extension study of 10% to 20%, it is expected to achieve a maximum of 300 to 340 evaluable participants for the extension study.

Study Intervention Groups and Duration: The extension study will cover a 2-year period in which the participants will not be treated with cladribine tablets, which were administered in the CLARIFY MS trial.

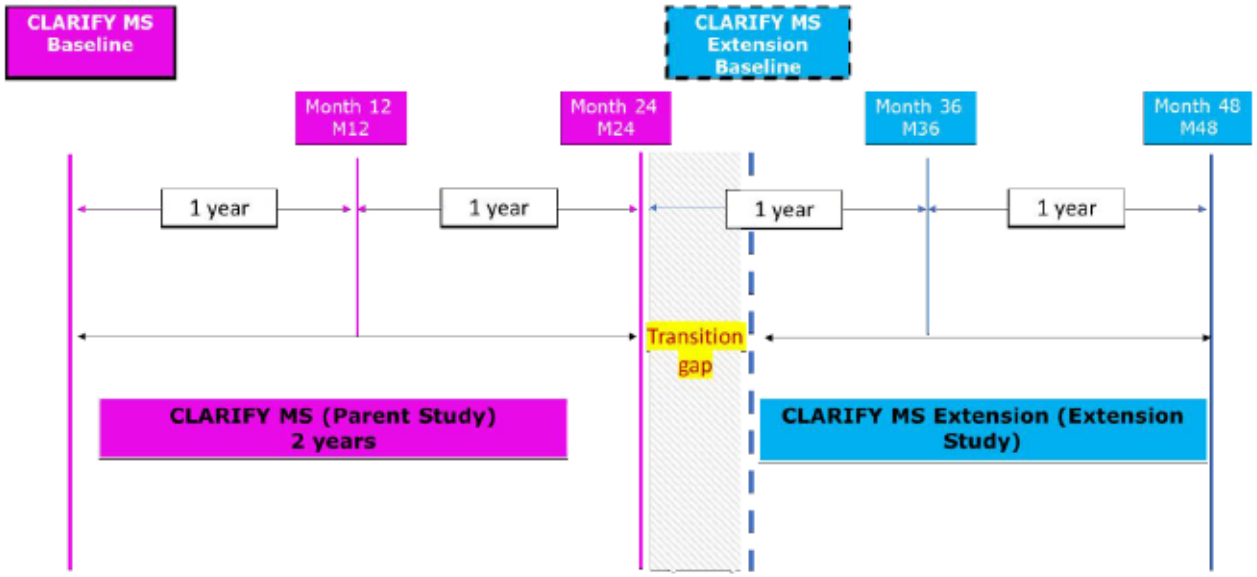
Involvement of Special Committee(s): Yes

A Steering Committee (SC) will be established; 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, the conduct, and the evaluation of the study. The SC is responsible for safeguarding the interests of participants and for the conduct of the study.

1.2 Schema

A schema of the study design, including both CLARIFY MS (parent study) and CLARIFY MS Extension (extension study), is presented below.

Figure 1: Study Schema



Note: M36 and M48 will be planned relative to CLARIFY MS Baseline; a potential delay in M24 (i.e., the Final Study Visit of the CLARIFY MS trial) due to a delay in the initiation of the second-year cladribine tablet treatment does not affect the timing of M36 and M48.
Baseline of the extension study will include retrospective data collection from the potential transition gap (i.e., period between M24 and CLARIFY MS Extension Baseline) and prospective assessments.

1.3 Schedule of Activities

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

Table 2 Schedule of Activities

Assessments & Procedures	Assessment Period					Notes
	Baseline	M36	End of Study/ M48	Unscheduled Visits	Early Dis-continuation Visit	
Study month (from initial administration of cladribine tablets) Visit window	Between CLARIFY MS Final Visit (M24) and M36	36 ± 28 days	48 ± 28 days	24-48		
Informed Consent	X					
Inclusion/exclusion criteria	X					
Demography	X					
Medical history	X					For medical history, only serious adverse events (SAEs) which are ongoing from the CLARIFY MS trial will be recorded (as described in Section 8.3.1)
Concomitant medications and procedures	X	X	X	X	X	Baseline data will be collected retrospectively from the transition gap between CLARIFY MS Final Visit (M24) and CLARIFY MS Extension Baseline for any concomitant medications that may have been initiated in that time period
Cognitive Function						
CCI [redacted]			[redacted]		[redacted]	[redacted]
HRQoL						
Multiple Sclerosis Quality of Life 54 - Instrument (MSQoL-54)		X	X		X	
CCI [redacted]		[redacted]	[redacted]		[redacted]	
COVID-19 Survey		X	X		X	
Employment Status			X		X	

Assessments & Procedures	Assessment Period					Notes
	Baseline	M36	End of Study/ M48	Unscheduled Visits	Early Dis-continuation Visit	
Safety Assessments						
Physical examination		X	X	X	X	
Vital signs		X	X	X	X	
Adverse event reporting	X	X	X	X	X	Baseline data will be collected retrospectively from the transition gap between CLARIFY MS Final Visit (M24) and CLARIFY MS Extension Baseline for any AEs and SAEs that may have occurred in that time period
Disability						
[redacted]	[redacted]	[redacted]	[redacted]		[redacted]	CCI [redacted]
[redacted]		[redacted]	[redacted]		[redacted]	
[redacted]		[redacted]	[redacted]		[redacted]	
[redacted]		[redacted]			[redacted]	[redacted]
Relapse report	X	X	X		X	Baseline data will be collected retrospectively from the transition gap between CLARIFY MS Final Visit (M24) and CLARIFY MS Extension Baseline for any relapses that may have occurred in that time period
CCI [redacted]		[redacted]	[redacted]		[redacted]	
CCI [redacted]	[redacted]					CCI [redacted]

Assessments & Procedures	Assessment Period					Notes
	Baseline	M36	End of Study/ M48	Unscheduled Visits	Early Dis-continuation Visit	
CCI					CCI	
Patient diary	Continuously					To be filled out by the participant in a continuous manner

CCI ; AE=Adverse event; CCI ; COVID-19=Corona Virus Disease 2019; CCI ; HRQoL=Health related quality of life; CCI ; CCI ; MS=Multiple Sclerosis; MSQoL-54=Multiple Sclerosis Quality of Life 54 Questionnaire; CCI ; SAE=Severe adverse event; CCI

2 Introduction

Cladribine tablets (Mavenclad®) are 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 cladribine tablets is in the Summary of Product Characteristics (SmPC).

2.1 Study Rationale

Highly-active RMS is characterized by neurological deterioration causing motor and cognitive dysfunction and impacting health related quality of life (HRQoL) (Jones 2016). Whilst 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 will add to the evidence by investigating the long-term effect (over 2 years after initiation of treatment) on cognition and patient-reported outcomes (PROs) among adults with highly-active RMS. This extension study will collect 2-year follow-up data to the CLARIFY MS trial till up to 4 years after initial dose of cladribine tablets to explore the long-term effects of cladribine tablet administration.

For further information on study rationale, please refer to Section 4.2.

2.2 Background

Multiple sclerosis (MS) 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).

Some patients experience a highly-active disease course with rapid and early 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).

Despite the recent approvals of several newer therapies, the treatment burden of MS remains significant. While clinical studies demonstrate evidence for the efficacy of new therapies, 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 as well as the potential impact on cognitive impairment and HRQoL by new drugs in MS patients.

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 Multiple Sclerosis (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).

Efficacy data from the CLARITY trial showed a statistically significant lower annualized relapse rate (ARR), higher proportion of patients relapse-free over 96 weeks, higher proportion of patients free of sustained disability over 96 weeks, and longer time to 3-month EDSS progression in participants receiving cladribine tablets 3.5 mg/kg compared to participants on placebo (Giovannoni 2010). In addition, cladribine tablets were statistically significantly superior to placebo with regard to numbers 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 primary aim of this study is to assess cognition and HRQoL over the third and fourth year after 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 benefit/risk relationship was carefully considered in the planning of this extension study. More detailed information about the known and expected benefits and risks and reasonably expected adverse events (AEs) of cladribine tablets may be found in Section 4.2 and the SmPC. Also, during the CLARIFY MS trial, study participants received cladribine tablets, which were considered to have a positive benefit/risk profile that supported their use in this participant group. Minimal risk to participants is expected since participants enrolled in this study will not be receiving any study treatment; the cladribine tablets treatment course is to be completed under the study protocol of the CLARIFY MS trial, and participants will receive routine clinical care over the extension study period. The CLARIFY MS Extension study will be of an interventional nature, because of the MRI scans, blood draws, and PROs, as per study protocol. 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.

CCI [redacted]

Blood draws may cause discomfort, bruising, and very rarely infection at the site where the skin is punctured by the needle. Patients 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.

3 Objectives and Endpoints

The study objectives and their linked endpoints are described in Table 3. For the statistical aspects of the endpoints, refer to Section 9.4.

Table 3 Study Objectives

Objectives	Endpoints
Primary	
To assess cognitive impairment in participants with highly-active RMS, having participated in the CLARIFY MS trial, at 4 years after initial dose of cladribine tablets	Percentage of participants with no or minimal decline in cognitive function, defined as an improved or stable Symbol Digit Modalities Test (SDMT) score[a] or a decline of 4 points or less in the SDMT score, at 4 years after initial dose of cladribine tablets (M48) compared to SDMT score prior to initial dose of cladribine tablets (CLARIFY MS Baseline)
Secondary	
To assess health related quality of life (HRQoL) in participants with highly-active RMS, having participated in the CLARIFY MS trial, at 4 years after initial dose of cladribine tablets	• Change in HRQoL as measured by Multiple Sclerosis Quality of Life 54 Questionnaire (MSQoL-54) physical and mental health scores at 4 years after initial dose of cladribine tablets (M48) compared to prior to initial dose of cladribine tablets (CLARIFY MS Baseline) • Change in HRQoL as measured by MSQoL-54 physical and mental health scores at 4 years after initial dose of cladribine tablets (M48) compared to M24
CCI [redacted]	
To assess the long-term (4 years) safety and tolerability of cladribine tablets	• Occurrences of adverse events (AEs) and serious adverse events (SAEs) during the third and fourth year after initial dose of cladribine tablets
CCI [redacted]	[redacted]

Objectives	Endpoints
CCI	[redacted]

Objectives	Endpoints
CCI	

Objectives	Endpoints
CCI	

CCI CCI Visuospatial Memory Test-Revised; CVLT-II=California Verbal Learning Test-II; CCI ; HRQoL=Health related quality of life; CCI ; MS=Multiple Sclerosis; MSQoL-54=Multiple Sclerosis Quality of Life 54 Questionnaire; CCI RMS=Relapsing Multiple Sclerosis; SAE=Serious adverse event; CCI ; CCI .

CCI

4 Study Design

4.1 Overall Design

- This will be an open label, single arm, exploratory, multicenter, retrospective and prospective, 2-year Phase IV extension study, of participants with highly-active RMS who completed the CLARIFY MS trial (EudraCT no.: 2017-002632-17).
- The CLARIFY MS trial was a single arm, open label, multicenter, 2-year Phase IV study of participants who received cladribine tablets for 2 years, with one treatment course of 2 weeks at the beginning of each year. The Final Study Visit of the CLARIFY MS trial (M24) is planned 12 months after the initiation of the second-year treatment; initiation of the second-year treatment is planned 12 months after initial dose of cladribine tablets, but could be delayed due to, for instance, lymphocyte count below expected ranges.
- The extension study involves the follow-up of participants for an additional 2-year period (until 4 years after initial administration of cladribine tablets), during which the participants are not treated with cladribine tablets. The aim is to include participants from countries with at least 20 participants enrolled in the CLARIFY MS trial or sites with at least 10 participants enrolled in the CLARIFY MS trial.
- The extension study Baseline will be planned as near to M24 as possible; the extension study Baseline may also be the same visit as M24. At Baseline, data will be collected retrospectively from the potential transition gap period between M24 and CLARIFY MS Extension Baseline, and prospective data will be collected as per Schedule of Activities (Section 1.3). Informed consent for participation in the extension study needs to be obtained before any assessments which are specific to the extension study.
- Participants will attend visits for assessments, including the extension study Baseline, M36 at 36 months/3 years since initial dose of cladribine tablets, and M48 at 48 months/4 years since initial dose of cladribine tablets. The visits should be planned as close to the yearly date as possible, but as a maximum, fall within a window of ±28 days. A participant may return for an Unscheduled Visit at the discretion of the Investigator to undergo further evaluations. The data from Scheduled and Unscheduled Visits will be collected in the electronic case report form (eCRF).
- In the event of early discontinuation from the extension study, the participant will be invited to return for the Early Discontinuation Visit for final assessment. In case the participant is not willing to or cannot return to the site for the Early Discontinuation Visit, a telephone call will be organized to obtain the reason for withdrawal and AE reporting.
- The schema and visit schedules for efficacy and safety assessments are detailed in Sections 1.2 and 1.3.
- The study aims to enroll the first participant in Q1 2021 and have the last participant's visit in Q4 2023.
- A Scientific Steering Committee (SC) will be established to ensure that the study meets scientific standards (Refer to Appendix 2).

4.2 Scientific Rationale for Study Design

The treatment burden of MS is significant and further evidence for the long-term effect of new therapies is needed (Derfuss 2020; Lucchetta 2020). This extension study of the CLARIFY MS trial will contribute to the knowledge on the long-term effect and safety of cladribine tablets for the third and fourth year after initiation of treatment, focusing on cognition and HRQoL, among adults with highly-active RMS.

Cladribine tablets treatment has a maximum duration of 20 days in 2 years, after which participants are to be monitored according to the SmPC for an additional 2 years (treatment-free). The design of this extension study is based on this cladribine tablet treatment-free monitoring period, with the participants visiting Investigators as part of routine clinical practice; most assessments are part of routine clinical practice, CCI [redacted]

The primary objective of this study is to assess cognition in participants with highly-active RMS at 4 years after initial dose of cladribine tablets. Participants with highly-active RMS are at high risk for early cognitive impairment. The prevalence of cognitive impairment in MS is reported to be around 43% to 70%. Cognitive impairment has a detrimental effect on the lives of MS patients by reducing social activities, increasing physical dependence, retarding progress in rehabilitation, and affecting everyday life activities (Langdon 2010).

To assess cognitive function over the study period, an expert consensus committee of neurologists and neuropsychologists, with extensive research and clinical experience of MS cognition, have recommended CCI [redacted]. The CCI is a universally accepted assessment for cognitive function in MS that takes a short time to administer, is highly sensitive and reliable, and healthcare professionals can easily be trained to administer it, whereas qualified neuropsychologists are required for other similar assessments (Benedict 2012). The CCI ; a CCI component has been correlated to CCI [redacted] (Batista 2012). The CCI is collected routinely in MS care in all participating countries, while the other components of CCI are not, as they have not been validated yet in some of the participating countries (including Austria, the Netherlands, and Denmark).

The secondary objective of this study is to assess HRQoL in participants with highly-active RMS at 4 years after initial dose of cladribine tablets. The HRQoL of patients with MS is lower than patients with any other chronic conditions, including ischemic heart disease, Type-2 diabetes, and Crohn's disease (Orme 2007). The Multiple Sclerosis Quality of Life 54 Questionnaire (MSQoL-54) is an ideal questionnaire to assess HRQoL in MS patients over a period of time, because it can address the impact of the low burden of treatment of cladribine tablets in overall HRQoL, which covers multiple domains, including role limitations, bodily pain, physical function, emotional wellbeing, energy, health perceptions, social function, cognitive function, health distress, sexual function, change in health, and overall quality of life.

Furthermore, an important CCI [redacted]

In addition, while the efficacy of cladribine tablets on relapses and disease progression and safety have been demonstrated in previous clinical studies, evidence of efficacy and safety at the third and fourth year in patients with highly-active RMS in a real-world setting (cladribine tablets administration as per SmPC) is relatively limited. CCI [redacted] are included as they play an important role in the management and monitoring of patients with MS (Oreja-Guevara 2015) and have provided important outcomes in previous cladribine tablets clinical studies.

Moreover, CCI [redacted] may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to CCI [redacted] determinants that could impact cladribine tablet absorption, distribution, metabolism and excretion; mechanism of action of cladribine tablets; disease etiology; and/or molecular subtype of the disease being treated. CCI [redacted]

The current pandemic due to the coronavirus disease 2019 (COVID-19), attributable to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a major impact on clinical care and patients' lives (Stojanov 2020). Consequently, there may also be an impact on the study endpoints, in particular on HRQoL. To account for the potential impact of this pandemic, participants will be asked to fill out a COVID-19 Survey (Section 8.1.3).

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 scheduled procedure in the End of Study Visit (M48), as 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 having participated in the CLARIFY MS trial, who
   a. Have at least CLARIFY MS Baseline data on SDMT
   b. Received at least a single dose of cladribine tablets in the CLARIFY MS trial
   c. Completed the Final Study Visit (M24) of the CLARIFY MS trial.
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 and Sponsor, 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 serious adverse event (SAE), which were initiated during the CLARIFY MS trial, and are ongoing at the time of enrolling (i.e., signing the informed consent) in the extension study.
- Concomitant therapies that were initiated after the Final Study Visit of the CLARIFY MS trial (M24) and prior to enrolling (i.e., signing the informed consent) in the extension study.

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

There are no restrictions regarding concomitant therapies that a participant can be on during the study period; participants will be treated at the discretion of the Investigator.

- Disease-related: All concomitant medications used for conditions / symptoms related to MS (for example, pain, fatigue or weakness, incoordination, bladder dysfunction, spasticity).
- Medical history related: All concomitant medications used for a medical condition already reported in the participant's medical history (for example, any form of pain, especially lower back pain and headache, depression etc.) 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 the 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 8.1.7.1), treatment will be at the discretion of the Investigator, following local good medical practice and international guidelines.
- Disease reactivation: In the case of disease reactivation, further disease-modifying treatment will be at the discretion of the Investigator.
- Prohibited medicines: As per SmPC for cladribine tablets.

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, an option for a telephone call is provided, to obtain reason for discontinuation and the safety assessment at least.
- 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 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 Subject ID Number (if possible, the same as in the CLARIFY MS trial).
- Baseline information including demography (date of birth, gender, and race), medical history, and disease (MS) status and disease history will be obtained from the CLARIFY MS trial.
- The results of the assessments and procedures will be stored in the extension study electronic data capture (EDC) system. 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 extension 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 identifiable information.
- For MSQoL-54, CCI , and the CCI CCI ePROs will be used. The ePROs will be migrated to an app-based solution, which allows text and scale questions to be configured to maintain the validity of the assessment.
- The COVID-19 Survey will be a paper-based questionnaire. The participant will fill out the survey at the site and the Investigator will enter the data into the EDC.
- This study will be monitored in accordance with the International Council for Harmonization's Good Clinical Practice (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 15 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.

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.

During the extension study Baseline Visit, the participants will be informed of the study objectives and overall requirements, and informed consent will be obtained prior to any assessments specific to the extension study (see Appendix 2 for details on informed consent process).

The PROs must be performed prior to clinical assessments at all visits. CCI . MSQoL-54 is to be completed by the participant on a hand-held tablet device, on-site at the clinic; the CCI questionnaires will be filled in at home on

a monthly basis and may be filled out at the site if the visit aligns with the monthly CCI assessments. The tablet device used in this study will be the Apple iPAD Air 2. Participants can ask for assistance in operating the device and accessing the questionnaires. Responsible Site staff will be trained on these ePROs (MSQoL-54, CCI and the CCI questionnaires) before first test implementation to participants.

Assessments related to CCI should be done by the Investigator. It is not needed to have separate rater for neurological assessments.

Training modules are recommended for the sites about the assessments for sake of low inter- rater variability. Whenever possible, the same assessor should manage the same participant for these scales.

In addition, the Investigator will collect the participant's employment status. Procedures for the CCI and blood draws at the site are described in separate documents (CCI scan user's manual and the Laboratory Manual).

8.1.1 Cognition

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8.1.2 Health Related Quality of Life

8.1.2.1 Multiple Sclerosis Quality of Life-54 Instrument

The MSQoL-54 questionnaire will be completed by the participants on the tablet at the site. The MSQoL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument (Vickrey 1995; Vickrey 1997). The MSQoL-54 questionnaire was developed to measure HRQoL in patients with MS. It is composed of 54 items and is a combination of the SF-36 as well as an additional 18 disease-specific items such as fatigue and cognitive function. Validated translated versions will be used in applicable countries.

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8.1.3 COVID-19 Survey

The COVID-19 Survey will collect information on:

- Participants' potential infection(s) with COVID-19 since the beginning of the pandemic and the severity of the symptoms
- Infections and/or mortality due to COVID-19 in the participants' family and social environment
- Potential quarantine periods and lockdowns
- Participants' perceived impact of lockdowns on professional and social activities
- Participants' stress level related to lockdown and mandatory social restrictions

8.1.4 Employment Status

The Investigator will collect the participant's employment status to classify in one of the 6 available employment conditions: Unemployed, Sick leave, Employed/ part time, Employed/full time, Education, Homemaker.

8.1.5 Disability Assessments

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8.1.7 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 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).

8.1.7.1 Relapse Evaluation

All the following criteria are to be met for establishing an MS clinical relapse (i.e., qualifying 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 > 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.

8.1.7.2 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 patient diary will be reviewed, and 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 a 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 a relapse during the course of the study is fulfilled.

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8.1.10 Patient Diary

The participants will be provided with access to a diary to record details on AEs and concomitant medications and procedures. The participants will receive instructions regarding the filling out of the diary.

The participant's 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 what each participant records on his/her form and any information that is obtained after subsequent questioning of the participants.

8.1.11 Retrospective Data Collection

Previous measurements of efficacy assessments, performed as part of the CLARIFY MS trial, will be retrieved in the analysis phase.

8.2 Safety Assessments and Procedures

The safety profile of cladribine tablets will be assessed through the recording, reporting and analysis of baseline medical conditions, AEs, physical examination findings, and vital signs. At each Study Visit (Section 1.3), the participant will be queried on changes in his or her disease condition and the patient diary will be reviewed for any AEs that may have occurred between the visits. 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 3. More information can be found in Appendix 3 and in the CRF Completion and Monitoring Conventions provided by the Sponsor.

8.2.1 Physical Examinations

- At the discretion of the physician, a complete or brief physical examination will be performed:
    - 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, pulse, and respiratory rate.

8.3 Adverse Events and Serious Adverse Events

- In this section, "study intervention" refers to cladribine tablets (i.e., the study intervention of the CLARIFY MS parent study) since no study intervention is administered in this study.
- The definitions of an AE and a SAE are in Appendix 3.
- 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 M48 (End of Study Visit) or Early Discontinuation 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 M48 (End of Study Visit) or Early Discontinuation Visit at the time points specified in the Schedule of Activities.
- The date of the last procedure according to the CLARIFY MS trial (i.e., the CLARIFY MS exit date) and the date of signing informed consent for the CLARIFY MS Extension study (i.e., the CLARIFY MS Extension enrollment date) are important to determine how AEs/SAEs will be recorded and reported:
  - SAEs with an onset date prior to the CLARIFY MS exit date and are ongoing on the CLARIFY MS Extension enrollment date will be recorded on the Medical History/Current Medical Conditions CRF. If the event worsens, a new SAE will be recorded on the AE CRF page and reported as specified in Appendix 3. Non-serious AEs which are ongoing at the CLARIFY MS exit date will not be recorded in the CLARIFY MS Extension study.
  - AE/SAEs with an onset date after the CLARIFY MS exit date and before the CLARIFY MS Extension enrollment date will be collected retrospectively (after obtaining informed consent) and recorded on the AE CRF page for the CLARIFY MS Extension study.
  - AEs/SAEs with an onset date after the CLARIFY MS Extension enrollment date will be recorded on the AE CRF page for the CLARIFY MS 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 3. 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 interventions 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 should be 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 3.

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 3.

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 signing of the ICF until M48 (End of Study Visit) or Early Discontinuation Visit, as per the Schedule of Activities (Section 1.3). Based on known pharmacological effects of cladribine tablets and

mechanism of action, no pregnancy data from female partners of male participants will be collected during this study since no cladribine tablet treatment is administered.

- 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.
- Pregnancies with an onset date after the CLARIFY MS exit date and before the CLARIFY MS Extension enrollment date will be collected retrospectively after obtaining informed consent for the CLARIFY MS Extension study. The pregnancy, of which the Investigator learned at enrollment, should be reported to the Sponsor within 24 hours after patient signed informed consent for CLARIFY MS Extension study.

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 or if she became pregnant during the gap period between CLARIFY MS Final Visit (M24) and CLARIFY MS Extension Baseline. The initial information will be recorded on the AE CRF page and submitted to the Sponsor using the applicable paper report form. The report should be submitted within the timelines described above.
- 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 treatment is involved, and the assessments are either part of routine medical care, non-invasive PROs, or non-extensive blood samples. In addition, participants who switch to any other disease-modifying drug, appropriate safety and contraception measures will be followed as per the new disease-modifying drug's SmPC and local clinical practice.

8.3.6 Disease-Related Events and/or Disease-Related Outcomes not Qualifying as Adverse Events or Serious Adverse Events

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.

8.3.7 Adverse Events of Special Interest

Not applicable.

8.4 Treatment of Overdose

Not applicable.

8.5 Pharmacokinetics

Not applicable.

8.6 Pharmacodynamics

Not applicable.

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8.9 Immunogenicity Assessments

Not applicable.

9 Statistical Considerations

The statistical analyses described in this section will be performed as further outlined in the Integrated Analysis Plan (IAP), which will be finalized prior to database lock and will be included in the CSR for this protocol.

Study data will be integrated with study data from the CLARIFY MS trial as required to perform the statistical analyses.

Continuous variables will be summarized using descriptive statistics, i.e., number of participants, number of participants with missing and non-missing values, mean, standard deviation, median, 25th Percentile, 75th Percentile (Q1-Q3), minimum, and maximum. Qualitative variables will be summarized by counts and percentages.

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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
Screening Set	All participants who provided informed consent for the extension study
Full Analysis Set (FAS)	The FAS will include all eligible participants
Safety Analysis Population	The Safety Analysis Set will include all participants from the Screening Set who received at least one dose of cladribine tablets

FAS=Full analysis set.

The efficacy analyses will be performed on the Full Analysis Set (FAS). All safety analyses will be performed on the Safety Analysis Population.

9.4 Statistical Analyses

The study is exploratory in nature. A control of the potential Type-I-error inflation caused by multiple endpoints and multiple testing is not implemented.

Parameter estimates with associated 95% confidence intervals will be reported, as applicable.

The study dataset comprises of multiple outcome assessments made for each participant over a 24-month period. 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 trigger the approach to deal with missing data.

9.4.1 Efficacy Analyses

The efficacy analyses are described in Table 6. All efficacy analyses will be performed on the FAS population.

Table 6 Analysis of Efficacy Endpoints

Endpoint	Statistical Analysis Methods
Primary	The proportion of participants with no decline or a maximal decline of 4 points in SDMT score at M48 will be described using a 95% confidence interval computed according to Wilson's score method. A logistic regression with at least age and Baseline EDSS included as covariates will be performed as sensitivity analysis. Further factors or covariates to predict disease progression may be added as appropriate. In order to investigate the robustness of results of the primary efficacy analysis with respect to missing values, additional sensitivity analyses will be conducted by applying multiple imputation techniques. The impact of different assumptions with regards to missing patterns will be investigated.
Secondary	The differences in MSQoL-54 physical and mental health scores at M48 will be assessed using repeated mixed-effects linear regression, accounting for clinically relevant factors (e.g., age and EDSS), within-participant correlation, and pooled center correlation. Estimates for the mean difference in scores between specified time points will be reported, with a 95% confidence interval and 2-sided p-value.
CCI	[redacted]
CCI	[redacted]

CCI [redacted] HRQoL= Health related quality of life; IAP=Integrated analysis plan; MS=Multiple sclerosis; MSQoL-54=Multiple Sclerosis Quality of Life 54 Questionnaire; CCI [redacted]

9.4.2 Safety Analyses

The safety analyses are described in Table 7. All safety analyses will be performed on the Safety Analysis Population. AEs and SAEs will be coded using Medical Dictionary of Regulatory Activities (MedDRA).

Table 7 Description of Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	Not applicable
Secondary	Not applicable
CCI [redacted]	[redacted]

AE=Adverse event; MedDRA=Medical Dictionary of Regulatory Activities; SAE=Serious adverse event.

9.4.3 Other Analyses

Participants' demographic factors and extension study Baseline clinical characteristics will be summarized.

The data collected with the COVID-19 Survey will be analyzed as additional explanatory variables to the efficacy analyses by possible impacts of the pandemic.

As the extension Study Visits are initiated 2 years after the initial treatment with cladribine tablets, it cannot be excluded that a specific type of participant from the CLARIFY MS trial is available for follow-up. A potential selection bias will be evaluated by comparing the characteristics of the participants from the CLARIFY MS trial and the participants included in this study.

9.4.4 Sequence of Analyses

Final analyses will be performed at the end of study. In addition, interim analysis at extension study Baseline or M36 may be performed.

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11 Appendices

Appendix 1 Abbreviations

CCI	[redacted]
AE	Adverse Event
CCI	[redacted]
CCI	[redacted]
BVMT-R	Brief Visuospatial Memory Test-Revised
COVID-19	Coronavirus Disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
CUA	Combined Unique Active
CVLT-II	California Verbal Learning Test-II
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
CCI	[redacted]
FAS	Full Analysis Set
GCP	Good Clinical Practice
CCI	[redacted]
CCI	[redacted]
HRQoL	Health Related Quality of Life
ICH	International Council for Harmonization
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISMP	Integrated Study Management Plan
CCI	[redacted]
MedDRA	Medical Dictionary of Regulatory Activities
CCI	[redacted]
MS	Multiple Sclerosis
MSQoL-54	Multiple Sclerosis Quality of Life-54 Questionnaire
CCI	[redacted]

CCI [redacted]	[redacted]
PRO	Patient-Reported Outcome
CCI [redacted]	[redacted]
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Steering Committee
CCI [redacted]	[redacted]
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reactions
CCI [redacted]	[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 (where allowed by local laws and regulations) and answer all questions on the study.
- Participants will be informed that their participation is voluntary.
- Participants or their legally authorized representative (where allowed by local laws and regulations) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50; local regulations; International Council for Harmonization (ICH) guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the Institutional Review Board/Independent Ethics Committee (IRB/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 informed consent form (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. If possible, each participant will be assigned the same identifier as in the CLARIFY MS trial. 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 their 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 CLARIFY MS trial, from Europe (including the following countries: Austria, Czech Republic, Denmark, France, Hungary, Italy, Poland, Slovakia, Spain, and the Netherlands) will be approached for participation in this extension study. About 65 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 Good Clinical Practice (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 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 participants and for the conduct of the study.

Contract research organization

- Contract research organizations (CROs) and vendors will be involved in some 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).

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 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 KGaA 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 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 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 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 the MSQoL, CCI , and CCI questionnaires, 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 contract research organization(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.

Appendix 3 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 CLARIFY 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 Meeting 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 NOT 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 the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention. A reasonable alternative explanation will be available.
  - Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the 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 (IB) 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 Electronic data Capture (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 using the applicable paper report form.
- The applicable paper report 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.

CCI [redacted]

Appendix 5 Contraception

According to cladribine tablets (Mavenclad®) SmPC, there are no requirements regarding contraception that apply after 6 months since the last dose. At the moment of enrollment in the CLARIFY MS Extension study, participants will have completed treatment, with a lapse of more than 6 months since the last dose of cladribine tablets.

Appendix 6 Sponsor Signature Page

Study Title:	A 2-year follow-up study to assess cognition and health-related quality of life in participants with highly-active relapsing multiple sclerosis, having participated in the CLARIFY MS trial
Regulatory Agency Identifying Numbers:	2020-003874-30
Clinical Study Protocol Version:	28 June 2021/Version 2.0

I approve the design of the clinical study:

PPD

Signature

30.6.2021

Date of Signature

Name, academic degree:	PPD, MD, MSc
Function/Title:	PPD, Global Medical Affairs, Neurology & Immunology
Institution:	Merck Healthcare KGaA
Address:	Frankfurterstrasse 250. 64293, Darmstadt, Germany
Telephone number:	PPD
Fax number:	Not Applicable
E-mail address:	PPD

Appendix 7 Coordinating Investigator Signature Page

Study Title:	A 2-year follow-up study to assess cognition and health-related quality of life in participants with highly-active relapsing multiple sclerosis, having participated in the CLARIFY MS trial
Regulatory Agency Identifying Numbers:	2020-003874-30
Clinical Study Protocol Version:	28 June 2021/Version 2.0
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, ICH GCP (Topic E6) and all applicable Health Authority requirements and national laws.

PPD PPD PPD PPD

re

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

Appendix 8 Principal Investigator Signature Page

Study Title:	A 2-year follow-up study to assess cognition and health-related quality of life in participants with highly-active relapsing multiple sclerosis, having participated in the CLARIFY MS trial
Regulatory Agency Identifying Numbers:	2020-003874-30
Clinical Study Protocol Version:	28 June 2021/Version 2.0
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, ICH GCP (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: