Clinical Study Protocol

Title Page

Clinical Study Protocol Title:	Evaluating the Long-Term Outcomes and Durability of Effect Following Treatment with Cladribine Tablets for Multiple Sclerosis: An Exploratory Phase IV Ambispective Study of Patients Who Previously Participated in the CLARITY/CLARITY-EXT and ORACLE MS Clinical Trials
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Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	28 Jan 2019
2.0	Amended Protocol	03 July 2020

Protocol Version 2.0 (03-JUL-2020)

This amendment is nonsubstantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it neither significantly impacts the safety or physical/mental integrity of participants nor the scientific value of the study.

Overall Rationale for the Amendment

The changes implemented in the protocol have been undertaken in order to improve the quality and analytic plans for data collection, by clarifying study endpoints, the time windows for data collection, and the definitions of study subgroups.

Documentation of Protocol Amendments

Section # and name	Description of Change	Brief Rationale
Medical Responsible and Medical Monitor names	Change in the study physician.	Study physician has changed since the first protocol was written.
Section 1.1, Synopsis; Section 3, Objectives and Endpoints; Section 4.2, Scientific Rationale and Design; Section 9.4, Statistical Analysis	Updated definition of primary endpoint.	New definition to clarify and minimize ambiguity (per Steering Committee recommendation).
Section 1.1, Synopsis; Section 3, Objectives and Endpoints; Section 9.4, Statistical Analysis	Updated definition of secondary endpoint.	New definition to clarify and minimize ambiguity (per Steering Committee recommendation).
Section 1.1, Synopsis; Section 3, Objectives and Endpoints; Section 8.1.1.12, Cognition Endpoints	BVMT-R/SDMT: clarification was added for these assessments to be collected from ORACLE MS subjects only in countries where these instruments were approved for the use in the CLASSIC MS study	These instruments were only collected in countries where they had been previously used as part of data collection in the parent study; expansion to all participants would require additional ethical approval.
Section 1.1, Synopsis; Section 1.3, Schedule of Activities; Section 3, Objectives and Endpoints; Section 4.1, Overall Design; Section 4.2, Scientific Rationale and Design	Time window for collecting MRI and pharmacogenetic samples to be expanded to up to 3 months and up to 6 months, respectively.	Window extended to accommodate patient requests to provide samples/complete MRI at a later date than planned in first protocol, as long as occurring within expected study timeframe.
Section 1.1, Synopsis; Section 1.2, Schema; Section 1.3, Schedule of Activities; Section 4.1, Overall Design	Updated description of data collection windows and included an additional study schema (Figure 2) to reflect details of the updated time windows for 3 scenarios: patients without relapse at screening, patients with relapse at screening, and patients completing a remote visit. Additionally, new text was added to specify that it is possible to complete all assessments in a single day, and that patients undergoing relapse or suspected relapse could postpone Visit 1 (4 weeks to 3 months from baseline) as a stabilization period.	Clarify the different time windows that are applicable according to relapse status at baseline and specify the aim to collect the telephone EDSS within a comparable timeframe as the in-clinic EDSS among patients without relapse. Additionally, specification on potential to collect data in a single day was added to clarify acceptable practice for study sites. The change in time window between screening and visit 1 has been expanded to allow additional time for stabilization before Study Visit 1 in case of suspected relapses.
Section 1.1, Synopsis; Section 3, Objectives and Endpoints; Section 8.1.1.13, Brain Imaging	The volume of T1 lesions was added as a new endpoint among other MRI assessments being evaluated.	T1 lesion volume was omitted from the first protocol.

Section # and name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities	Vital signs added in the physical examination at Study Visit 1 in Schedule of Assessments.	Measurement was not included in the Schedule of Assessment table in first protocol.
Section 1.3, Schedule of Activities; Section 4.1, Overall Design; Section 8.1.1.1, Expanded Disability Status Scale (EDSS)	Clarify that in-person Expanded Disability Status Scale (EDSS) to be collected from patients coming to clinic for Study Visit 1, and telephone EDSS to be collected for patients participating remotely; both modes not required.	Reducing burden on patients and possible deviations from sites not doing both the assessments.
Section 1.3, Schedule of Activities	Indicate potential for remote screening assessment, pending local approval.	Avoid losing data collection among participants unable or unwilling to attend clinic visits.
Section 1.3, Schedule of Activities	Footnote added to clarify that the end of study form completion will occur at the last clinical visit (the later of Study Visit 1 or Study Visit 2).	Clarification of when this form is to be completed, particularly for the expanded data collection windows.
Section 2, Introduction	Added approval received by US FDA.	To reflect the updated status of drug's approval.
Section 4.1, Overall Design	Revision to enrolment dates.	Dates updated to reflect changes in study recruitment projections since first protocol.
Section 5.2, Exclusion criteria; Section 5.4, Screen Failures	Adjustment to study time windows in the situation of confirmed or suspected relapse.	Expanded data collection window to allow patient to stabilize and participate.
Section 6.5.4.2, MRI Sub-study	Specification that the MRI could be postponed among participants, but not beyond the time windows specified for the overall study.	Ensure there is no misunderstanding the MRI could be collected after the end of study (i.e. no later than 4 weeks after the last patient enrolled).
Section 6.5.4.2, MRI Sub-study	The definition of concomitant Cladribine (as an exclusion criterion for the MRI sub-study) was updated to reflect the availability of Cladribine by prescription, and to accommodate the shelf-life of Cladribine if received (through trial participation or prescription).	The timeline for concomitant Cladribine use was updated in relation to shelf-life and commercial availability (changed since the time of protocol version 1).
Section 8.3.5, Pregnancy	Clarify writing of section on pregnancies: information to be collected on prospective pregnancies, but only expedited reporting for MRI sub-study participants.	Guidance on requirements for collecting and reporting pregnancy data in full study versus MRI sub-study was not entirely clear in first version of protocol.
Section 9.3, Populations for Analysis	Definition of the subgroups for analysis updated: 1) Subgroup Treatment Course in Cohort B. 2) Subset Long-term responder 3) Prior use of DMD	1) Added details to the definition of subgroups according to treatment to clarify all subcategories are mutually exclusive and minimize ambiguity. 2) Clarification on addition details of long-term responders will minimize ambiguity 3) Prior use of DMD concern only CLARITY patients (Cohort B).

Section # and name	Description of Change	Brief Rationale
Section 9.4.2; Sequence of Analysis	Updated planned number of patients to be included in the planned Interim Analysis. Specified that pharmacogenetics and MRI would not be included in the interim analysis.	Planned final number of patients is unknown (enrolment is slow due to COVID-19 pandemic) and % can't be determined. 100 patients are considered minimum number for the interim analysis. The scope of data to be included in the IA required clarification to reflect the SAP.
Appendix 2, Study Governance	Additional text on date of study start and patient recruitment.	Updated as per Merck Template 14 (reflecting requirements of the TransCelerate and new EU-CTR updates).
Appendix 2, Study Governance	Details of the third-party service provider for MRI added.	These details were not listed in the first protocol.
Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Removed specification of expedited reporting of non-serious adverse events of special interest.	It is not a requirement to report non-serious adverse events within 24 hours.
Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Specification that a positive test for COVID-19 would be considered an AE.	This text was added to provide clarity for the sites, and was not applicable at the time of the first protocol
Appendix 3, Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting	Clarification on which form ADR data is to be captured on, according to timing of awareness of the event.	Reiterate guidance given to the sites to ensure correct data entry.
Throughout	Minor editorial and document formatting revisions.	Minor; therefore, have not been summarized.

1 Protocol Summary

1.1 Synopsis

Protocol Title: Evaluating the Long-Term Outcomes and Durability of Effect Following Treatment with Cladribine Tablets for Multiple Sclerosis: An Exploratory Phase IV Ambispective Study of Patients Who Previously Participated in the CLARITY/CLARITY-EXT and ORACLE MS Clinical Trials

Short Title: CLASSIC-MS

Rationale: The purpose of this study is to explore the long-term outcomes, durability of effect, and real-world treatment patterns in patients previously participating in the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials (i.e. parent studies). The results from this study may be of benefit to patients with multiple sclerosis (MS) and clinicians by helping to inform future treatment approaches and treatment decision-making.

Objectives and Endpoints: Data will be collected retrospectively and prospectively to evaluate the long-term outcomes, durability of effect, and real-world treatment patterns following treatment with Cladribine Tablets or placebo among patients with MS who were part of the parent studies. The objectives of this study are all exploratory and for hypothesis generating purposes.

Exploratory Objectives	Endpoints (Outcome Measures)
Primary	
To evaluate long-term mobility after treatment with an investigational medicinal product (IMP); Cladribine (Tablets or placebo) as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Proportion of study participants using a wheelchair (defined as unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day) the majority of the time in the 3 months prior to Study Visit 1 or participants are bedridden any time prior to Study Visit 1 determined via: 1). Expanded Disability Status Scale (EDSS) score of 7.0 or higher, or 2). Alternative clinical description data in medical records
Secondary	
To assess the long-term disability status after treatment with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Proportion of study participants with EDSS of 6.0 or higher as determined by EDSS documentation or alternative clinical description in medical records after last IMP from parent study.

Exploratory Objectives	Endpoints (Outcome Measures)
To evaluate differences in clinical characteristics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Clinical characteristics[a] at Study Visit 1 of long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to those of other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.
To evaluate differences in magnetic resonance imaging (MRI) characteristics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	MRI characteristics[c] at Study Visit 2 of long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to those of other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.
Tertiary	
To assess the real-world treatment patterns in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Time, type, and reason for first sequential treatment after first course[b] of IMP, type of second sequential treatment, as well as the frequency of routine clinical monitoring and disease activity status as well as clinical and demographic characteristics[a] available for the CLARITY/CLARITY-EXT and ORACLE MS populations.
To assess durability of clinical outcomes after treatment with IMP from Baseline (i.e. first dose[b] of IMP) to Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Tertiary endpoints to be evaluated via retrospective data collection from medical records or at Study Visit 1: • Proportion of study participants being bedridden[d] • Time from first dose[b] of IMP to first use of an ambulatory device[d] • Time from first dose[b] of IMP to first use of a wheelchair[d] • Annualized Relapse Rate (ARR) from time of first dose[b] of IMP to Study Visit 1, and by 2-year intervals • Time to conversion to Clinically Definite MS (CDMS) (For ORACLE MS study participants only)

Exploratory Objectives	Endpoints (Outcome Measures)
	• Proportion of study participants diagnosed as Secondary Progressive MS (SPMS) without relapses in the 3 months prior to SPMS diagnosis • Proportion of study participants diagnosed as SPMS with relapses in the 3 months prior to SPMS diagnosis • Proportion of study participants diagnosed as Primary Progressive MS (PPMS) (For ORACLE MS study participants only)
To assess impact on quality of life and cognitive outcomes after treatment with IMP during the period from the last clinical visit in the CLARITY/CLARITY-EXT/ORACLE MS clinical trials to Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Tertiary endpoints to be evaluated at Study Visit 1: • Change in EuroQoL-5 Dimension Questionnaire (3 level version) (EQ-5D-3L) • Change in cognition as measured by the following assessments (to be collected for ORACLE MS subjects only in countries where these instruments were used in the CLASSIC MS study): o The Brief Visuospatial Memory Test – Revised (BVMT-R) o Symbol Digit Modality Test (SDMT)
To assess durability of outcome on brain imaging after treatment with IMP from Baseline (i.e. the last MRI before first dose[b] of IMP; if feasible, by year) to within 3 months after Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	ORACLE MS, CLARITY and CLARITY-EXT study participants from selected sites will be invited to participate in a follow-up study visit (Study Visit 2) to take place within 3 months (maximum 4 weeks from Visit 1 after last patient enrolled) following Study Visit 1, for evaluation of the following: Change in MRI assessment from Baseline (i.e. the last MRI before first dose[b] of IMP) to Study Visit 2 in: • Total volume of T2 lesions • Total number of T2 lesions • Number of hypointense lesions on T1-spin echo MRI • Volume of hypointense lesions on T1-spin echo MRI • Brain volume or surrogate (in cases where brain volume is not possible to assess for technical reasons, then 3rd ventricle diameter may be evaluated) • Ventricular volume
To determine whether the high-disease activity (HDA) patients from the CLARITY/CLARITY-EXT clinical trials are more likely to be the long-term responders.	Comparison of the responder rate in HDA patients[e] versus the responder rate in non-HDA patients from the CLARITY/CLARITY-EXT population.

Exploratory Objectives	Endpoints (Outcome Measures)
To evaluate differences in genetics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Correlation of genetic variations with long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.

ARR=Annualized Relapse Rate, BVMT-R=Brief Visuospatial Memory Test Revised, CDMS=Clinically Definite Multiple Sclerosis, EDSS=Expanded Disability Status Scale, EQ-5D=EuroQoL-5 Dimension, HDA=High-disease activity, IMP=Investigational Medicinal Product, MRI=Magnetic Resonance Imaging, MS=Multiple Sclerosis, PPMS=Primary Progressive MS, RRMS=Relapsing-Remitting Multiple Sclerosis, SDMT=Symbol Digit Modalities Test, SPMS=Secondary Progressive Multiple Sclerosis.

[a] Specific clinical and demographic characteristics may include gender, age, race, ethnicity, education, disease duration, years previous disease modifying treatment (before start of CLARITY/CLARITY-EXT/ORACLE MS) and disease classification (RRMS or SPMS).

[b] One dose is equivalent to one tablet. One course of IMP is defined as 1 year of treatment with IMP (2 treatment cycles [weeks]). A treatment cycle is defined as daily administration of IMP given consecutively over 4-5 days during a 28-day period. One treatment week is equivalent to 1 treatment cycle.

[c] Total volume of T2 lesions; Total number of T2 lesions; Number of hypointense lesions on T1-spin echo MRI; Volume of hypointense lesions on T1-spin echo MRI; Brain volume or surrogate; Ventricular volume.

[d] Mobility endpoints may be determined via EDSS scores (if available) or corresponding clinical descriptions in medical records.

[e] 1. Patients with ≥2 relapses during the year prior to parent study entry, regardless of prior disease modifying drugs (DMD) use; 2. Patients with ≥1 relapse in the previous year and ≥1 T1 Gd+ lesions or ≥9 T2 lesions, while on therapy with other DMDs.

Overall Design: This Phase IV, low-interventional, multicenter, ambispective study will include study participants treated with Cladribine Tablets or placebo in the previously conducted parent studies. Long-term retrospective data will be collected through evaluation of medical charts/records (e.g., sociodemographic and clinical characteristics, medical and disease history, Secondary Progressive Multiple Sclerosis [SPMS] conversion, Expanded Disability Status Scale [EDSS], details of subsequent Disease Modifying Drugs (DMDs), including physician questions on treatment decisions, date of first use of an ambulatory device or wheelchair and relapse history from end of parent study to Study Visit 1 as well as, for ORACLE MS patients only, Clinically Definite MS conversion [CDMS] and Primary Progressive MS [PPMS] diagnosis).

Additional prospective data will be collected at Study Visit 1 (e.g., physical assessment, EDSS, Patient-Reported Outcomes [PRO], cognitive assessments). An optional blood sample for pharmacogenetic testing will be taken from patients who consent to the optional testing. A sub-study at Study Visit 2 involves a magnetic resonance imaging (MRI) scan without gadolinium in approximately 150 patients who are willing to participate in this MRI sub-study.

Number of Participants: No formal sample size calculation has been performed for this exploratory study as enrolment is limited to eligible study participants from the parent studies. Therefore, as many study participants as feasibly possible will be enrolled from this group. Additional considerations on the sample size of the study are included in Section 9.2.

Study Intervention Groups and Duration: No investigational medicinal product (IMP) will be administered as part of this study. The duration of the study for most patients is no more than 2 weeks from the time of the Screening Visit to Study Visit 1, except in the case of relapse at screening in which case the duration between Screening and Study Visit 1 is between 1 and 3 months. An optional blood sample will be collected at Study Visit 1from patients who consent to the optional pharmacogenetic testing. Pharmacogenetic testing may also occur during a subsequent clinical visit up to 6 months after the Screening Visit (unless last patient enrolled has occurred, in which case the testing must occur at Study Visit 1). For patients selected to participate in the MRI sub-study, an additional visit will be required (Study Visit 2) that will occur within a maximum of 3 months of Study Visit 1 (maximum 4 weeks from Study Visit 1 if last patient enrolment has occurred), and these patients' total study duration will be no more than 6 months. Sites will be asked to enter any retrospective data into the electronic case report form (eCRF) for this study within 12 weeks of enrolling the patient. Patients who are eligible will be given the option of completing screening, Study Visit 1 and 2 (where facilities for MRI are available) on the same day if prefer to do so and meet the eligibility criteria on that day (e.g. abstention from alcohol or cannabinoid products in the preceding 24 hours). Patients who are undergoing relapse or suspected relapse at the time of screening will be invited for Study Visit 1 after a stabilization period determined through consultation with the medical monitor.

Involvement of Special Committee(s): Yes.

1.2 Schema

Figure 1 represents an overall schematic of the exploratory study design. Figure 2 represents the different time windows according to subject relapse status at the time of screening, and for participants completing the study remotely. A detailed Schedule of Activities (SoA) is provided in Section 1.3.

Figure 1 Study Scheme

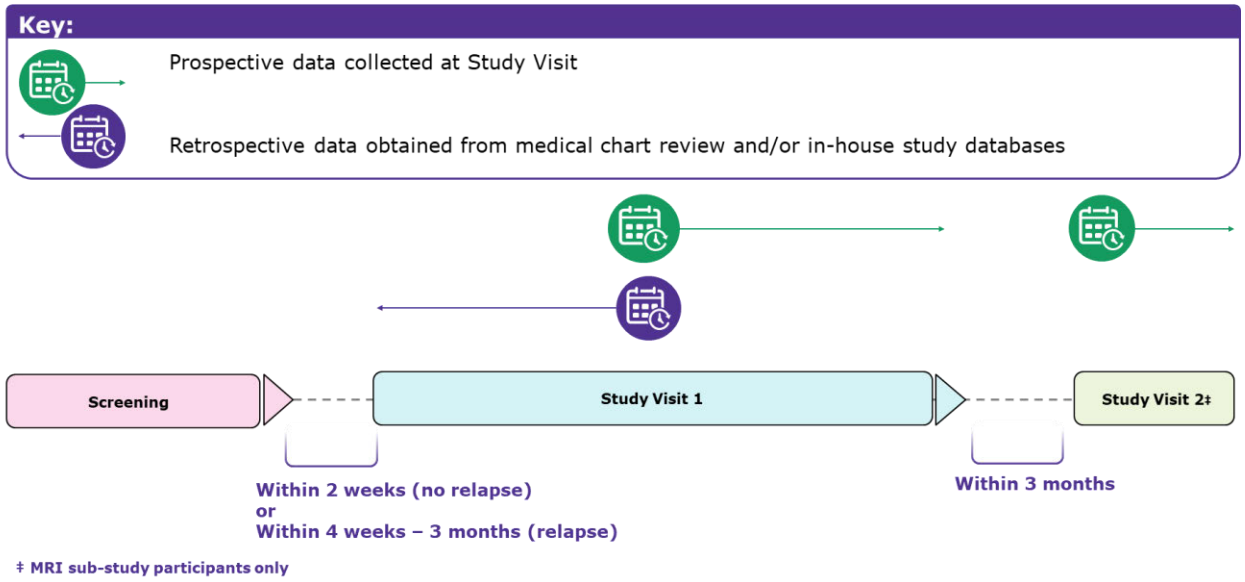
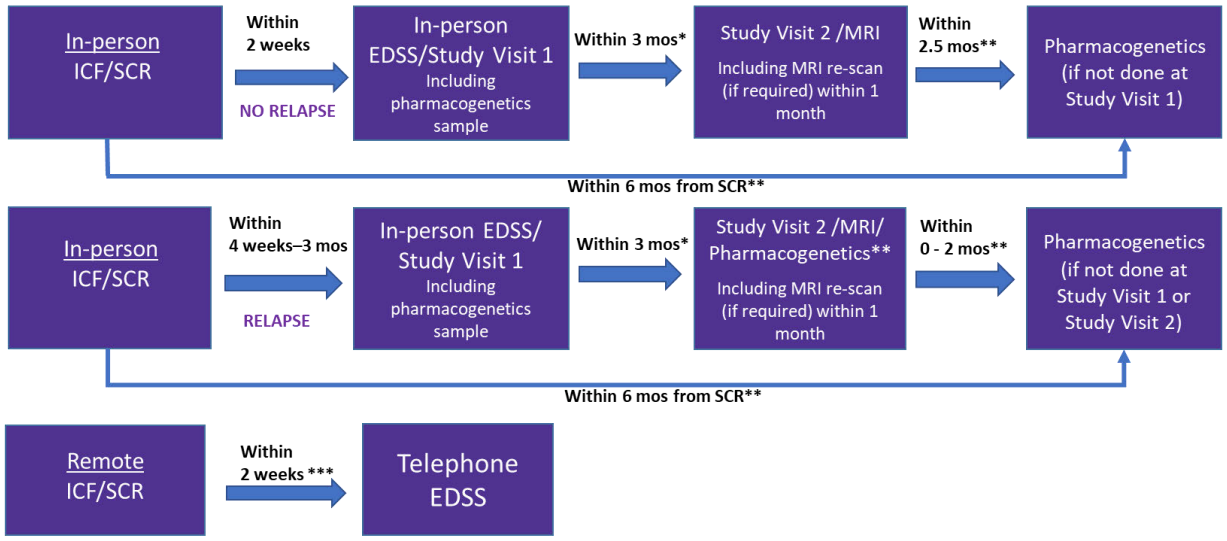


Figure 2 **Data collection time windows according to relapse status at recruitment and for remote visits**



* Within 3 mos from SV1 unless Last Subject Recruited, in which case no later than 4 weeks after.
** Within 6 mos from SCR unless Last Subject Recruited in which case no later than same day as SV1.
*** Within 2 weeks from ICF signatures.

EDSS = Expanded Disability Status Scale; ICF = Informed Consent; SCR = screening; MRI = magnetic resonance imaging

1.3 Schedule of Activities

Table 1 Schedule of Activities: Assessments Captured at Each Study Visit provides details on the SoA.

Table 1 Schedule of Activities: Assessments Captured at Each Study Visit

Assessments & Procedures	Screening	Study Visit 1	Study Visit 2	Notes
		Within 2 weeks of Screening **(in case of relapse: 4 weeks to 3 months)**	**Within 3 months[a] of Study Visit 1**	Screening assessments may be administered remotely if patient is unable to attend clinic for Study Visit, depending on approval by Ethics Committees (ECs), Institutional Review Boards (IRBs), and/or local regulations. Study Visit 1 time window does not apply if Screening and Study Visit 1 are combined.
Informed consent	X			If patient has passed away or is lost to follow-up, informed consent may be obtained from proxy/caregiver/legal representative, or an informed consent form (ICF) waiver may apply, depending on approval by ECs, IRBs, and/or local regulations.
Inclusion and exclusion criteria	X			
Sociodemographic and clinical characteristics	X			Includes parent study patient ID, gender, age/year of birth, race, ethnicity, employment status and education level attained, for sites where EC approval has been granted for collecting such data.
	Prospective data collection			
Physical examination including vital signs		X		
Expanded Disability Status Scale (EDSS): In-person (clinic visit) or telephone (remote visit only)[b]		X		The in-person EDSS is evaluated during Study Visit 1. The telephone EDSS is administered within 14 days after appropriate informed consent has been obtained, and is only to be collected for patients not attending in-person at Study Visit 1. Only 1 mode of EDSS administration (either in-person or by telephone) is required.

Assessments & Procedures	**Screening**	**Study Visit 1**	**Study Visit 2**	**Notes**
		Within 2 weeks of Screening **(in case of relapse: 4 weeks to 3 months)**	**Within 3 months[a] of Study Visit 1**	Screening assessments may be administered remotely if patient is unable to attend clinic for Study Visit, depending on approval by Ethics Committees (ECs), Institutional Review Boards (IRBs), and/or local regulations. Study Visit 1 time window does not apply if Screening and Study Visit 1 are combined.
EuroQoL-5 Dimensions (EQ-5D-3L)		X		
Brief Visuospatial Memory Test Revised (BVMT-R)		X		Administered only for ORACLE MS subjects only in countries where these instruments were used in CLASSIC MS study
Symbol Digit Modalities Test (SDMT)		X		
Optional blood sample for pharmacogenetic testing		X		In patients who consent to an optional blood draw and at sites with available capabilities to store and ship samples. The time window for pharmacogenetic sample collection is up to 6 months from Screening Visit (unless last patient enrolment has occurred, in which case the sample can only be collected at Study Visit 1).
Adverse events and concomitant medications		X	X	
End of study form [c]		X	X	
	Retrospective data collection (based on chart review)			
Medical and disease history	X			
EDSS from end of parent study to Study Visit 1		X		
Details of subsequent Disease Modifying Drugs (DMDs), including physician questions on treatment decisions		X		
Date of first use of an ambulatory device or wheelchair		X		

Assessments & Procedures	**Screening**	**Study Visit 1**	**Study Visit 2**		**Notes**
		Within 2 weeks of Screening **(in case of relapse: 4 weeks to 3 months)**	**Within 3 months[a] of Study Visit 1**		Screening assessments may be administered remotely if patient is unable to attend clinic for Study Visit, depending on approval by Ethics Committees (ECs), Institutional Review Boards (IRBs), and/or local regulations. Study Visit 1 time window does not apply if Screening and Study Visit 1 are combined.
Date of first time bedridden		X			
Relapse history from end of parent study to Study Visit 1		X			May be determined through retrospective chart review and/or at Study Visit 1, e.g. if conversion or disability progression occurred between last regular clinical visit and Study Visit 1; CDMS conversion and PPMS diagnosis are only assessed in ORACLE MS patients.
Secondary Progressive Multiple Sclerosis (SPMS) conversion		X			
Clinically Definite Multiple Sclerosis (CDMS) conversion		X			
Primary Progressive Multiple Sclerosis (PPMS) diagnosis		X			
Adverse drug reactions related to Cladribine Tablets		X			Any adverse drug reaction (ADR) that occurred after the End of Trial Visit in the parent study and is assessed as related to Cladribine Tablets by the Investigator must be recorded in the eCRF.
	MRI sub-study				
Urine pregnancy test			X		Urine pregnancy test to be conducted in female patients of childbearing potential participating in MRI sub-study within 1 week prior to the MRI assessment.
Magnetic Resonance Imaging (MRI) assessment			X		If a re-scan is required for the MRI assessment, this must be scheduled within one month of Visit 2; the scheduling of the re-scan cannot occur more than 4 weeks after Site Visit 1 if the last subject has been recruited.

ADR=Adverse Drug Reaction, BVMT-R=Brief Visuospatial Memory Test Revised, CDMS=Clinically Definite Multiple Sclerosis, DMD=Disease Modifying Drug, EC=Ethics Committee, eCRF=electronic Case Report Form, EDSS=Expanded Disability Status Scale, EQ-5D=EuroQoL-5 Dimensions, ICF=Informed Consent

Form, IRB=Institutional Review Board, MS=Multiple Sclerosis, MRI=Magnetic Resonance Imaging, PPMS=Primary Progressive Multiple Sclerosis, SDMT=Symbol Digit Modalities Test, SPMS=Secondary Progressive Multiple Sclerosis.

[a] Scheduling of Study Visit 2 cannot occur more than 4 weeks from Study Visit 1 if last subject has been recruited

[b] The in-person EDSS is a standardized physical neurological examination conducted in-person, including assessment of walking distance, whereas the telephone EDSS is a validated tool for telephone administration of the EDSS

[c] The Study Termination form will be completed at the date of MRI visit (Study Visit 2), or Study Visit 1, whichever is the last assessment for that patient.

2 Introduction

Despite the recent approvals of several newer therapies, the treatment burden of Multiple Sclerosis (MS) remains significant. The evidence of potential beneficial effects of new therapies are weak and studies are often of a short-term nature with little follow-up of original clinical trial participants (Tramacere, 2015).

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 (RRMS), across early to late stage studies as well as in treatment-naïve or treatment-experienced patients (Giovannoni, 2010; Leist, 2014; Section 2.2).

Cladribine (2-chloro-2'-deoxyadenosine [2-CdA]) is a synthetic anti-neoplastic drug that belongs to the subgroup of agents called purine analogs. Mavenclad® is approved (European Medical Agency [EMA] approval on 25th Aug 2017, and United States (US) Food and Drug Agency [FDA] on 29th March 2019) for the treatment of adult patients with highly active RRMS, as defined by clinical or imaging features, in:

- patients with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs (DMDs),
- patients with 2 or more relapses in the previous year, whether on DMD treatment or not.

Complete information on the chemistry, pharmacology, efficacy, and safety of Cladribine Tablets is in the Summary of Product Characteristics (SmPC) and/or the country specific label.

2.1 Study Rationale

The purpose of this study is to explore the long-term outcomes, durability of effect, and real-world treatment patterns in patients previously participating in the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials (i.e. parent studies). The 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. For Scientific Rationale for Study Design see Section 4.2.

2.2 Background

Epidemiology of Multiple Sclerosis

MS is a chronic, inflammatory, demyelinating disease of the central nervous system (CNS) and is the most common cause of serious neurological disability in young adults (Przybek, 2015). With no definite cause established, MS has been hypothesized to result from a complex interaction between individual genetic susceptibility and environmental factors that act as

triggers of a self-sustained auto-immune response (Noseworthy, 2000). With a peak of onset averaging at the age of 30 years in both genders, MS occurs predominantly in women with a female:male ratio of 3:1 (Kingwell, 2013).

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

Regarding incidence, globally, the median estimated incidence of MS is 2.5 per 100,000 person-years (PY) (Dua, 2008). Regionally, the median estimated incidence is greatest in Europe (3.8 per 100,000 PY) (Dua, 2008). The highest prevalence in Europe is 189 per 100,000 people in Sweden, and the lowest is 22 per 100,000 people in Albania (Multiple Sclerosis International Federation, 2013). In the United States, the incidence is estimated to be 3.2 per 100,000 PY (Multiple Sclerosis International Federation, 2013). Based on a recent study by the National Multiple Sclerosis Society, an estimated 947,000 people in the US have MS (Wallin, 2017).

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

Clinical Presentation and Categorization of MS

MS is not characterized by a singular, well-defined clinical presentation common to all patients with MS. The symptoms, which include a combination of cognitive, sensory and motor manifestations, vary among patients and throughout the disease course according to the affected CNS areas and the severity of the demyelinating attacks. Approximately 85% of patients with MS have initially RRMS (Multiple Sclerosis International Federation, 2013), which is characterized by alternating periodic acute exacerbations of disease activity (relapses) and periods of remission, consisting of partial or complete recovery (Lublin, 2014). The most important features of highly active RRMS include frequent relapses with incomplete recovery, and/or high radiological burden of disease, rapid accrual of disability after disease onset, with otherwise typical features of RRMS (Lublin, 2014). Data on the epidemiology of highly active RRMS is lacking and currently the proportion of patients that are classified as highly active comes from clinical trials. However, data show that around 14.4% to 14.8% of patients who had experienced breakthrough disease activity (≥ 1 relapse in the 12 months prior to randomization) (Gold, 2013; Rudick, 2006) and 22.2% of treatment-naïve patients (Polman, 2006) met the criteria for highly active RRMS (≥2 relapses in the year prior to study entry and ≥ 1 Gd+ lesion on T1- weighted MRI at study entry) (Gold, 2013; Rudick, 2006; Polman, 2006).

Treatment and Management of Relapsing Multiple Sclerosis

Patients with relapsing MS (RMS) are recommended to receive treatment with DMD to decrease the rate of relapse and slow the accumulation of brain lesions on MRI. Numerous immunomodulatory agents with differing routes of administration and mechanisms of action have been shown to have beneficial effects. Because they are not curative, most DMDs are typically continued indefinitely unless they are ineffective or not tolerated. There is currently no standard protocol to guide the choice of DMDs for patients with MS. Rather, treatment decisions and medication choices are the result of a thorough risk-benefit analysis and consideration of disease activity, patient-specific factors, and drug-related factors (Pardo, 2017).

Cladribine (2-chloro-2'-deoxyadenosine [2-CdA]) is a synthetic anti-neoplastic drug that belongs to the subgroup of agents called purine analogs. Cladribine Tablets have been approved by the EMA in 2017 for the treatment of adult MS patient with high active disease (see Section 2).

CLARITY Clinical Trial (NCT00213135)

In the Phase III, multi-center, randomized, double-blind CLARITY clinical trial (NCT00213135), treatment with Cladribine Tablets demonstrated a significant reduction in the annualized relapse rate (ARR) at 2 years from 0.33 to 0.14 when compared with placebo. This corresponded to an ARR risk reduction of 57.4% for the 3.5 mg/kg dose. The reduction in ARR was also consistent across various patient subgroups, including those with highly active disease. Furthermore, the CLARITY study demonstrated that Cladribine Tablets were significantly superior to placebo in the treatment of RRMS across all clinical and MRI efficacy outcomes (Giovannoni, 2010).

The CLARITY-EXT study showed that in patients who followed Cladribine Tablets with placebo, a substantial proportion remained free from indicators of disease activity, regardless of prior active treatment in CLARITY. Overall rates of (clinical and MRI) disease activity-free status were consistently high, although a longer treatment gap resulted in lower proportions of patients with no new T1 Gd+ lesions compared with those who had a shorter treatment gap (Comi, 2018).

ORACLE MS Clinical Trial (NCT00725985)

The ORACLE MS clinical trial (NCT00725985) was a Phase III, randomized, double-blind, placebo-controlled, multicenter, triple arm trial to evaluate the safety and efficacy of Cladribine Tablets in patients with early disease who had experienced a first clinical demyelinating event (FCDE) and who were at high risk of converting to CDMS, according to Poser criteria. Patients taking Cladribine Tablets (3.5 mg/kg) demonstrated statistically significant differences to the placebo group in the time to CDMS conversion during the initial treatment period up to the data cut-off (Leist, 2014).

Additionally, treatment with Cladribine Tablets significantly reduced the number of T1 Gd+ -enhanced lesions, new or enlarging T2 lesions, and combined unique active MRI lesions compared with placebo (Leist, 2014). Cladribine Tablets were associated with clinical and

MRI improvements versus placebo in patients with early RRMS (time to second event), active RRMS, and patients who were experiencing relapses despite ongoing interferon therapy (Comi, 2013; Comi, 2016; Freedman, 2017; Giovannoni, 2010; Giovannoni, 2016; Giovannoni, 2018; Leist, 2014; Montalban, 2016).

Based on these clinical trial results, Cladribine Tablets were approved for the treatment of RRMS in several markets. However, following negative Committee for Medicinal Products for Human Use opinion in 2011, Merck voluntarily withdrew further applications for approval as some regulatory authorities required more data to fully characterize the drug's benefit-risk profile. Consequently, there are a number of patients who received Cladribine Tablets prior to the earlier withdrawal. These patients have been followed in MS registries and observational studies for safety outcomes. The PREMIERE (Prospective Observational Long-term Safety Registry of Multiple Sclerosis Patients Who Have Participated in Cladribine Clinical Studies) study evaluated the safety of Cladribine Tablets over 10,000 PY of exposure in total, with follow-up in some patients exceeding 8 years at completion.

In August of 2017, the European Commission granted marketing authorization for Mavenclad® (Cladribine Tablets) for the treatment of highly active relapsing MS. The clinical program for cladribine in MS included more than 10,000 patient-years of data. This included 8,650 patient-years of cladribine exposure and more than 2,000 patient-years of placebo exposure (Cook , 2016).

Although the PREMIERE study provides long-term data following treatment with Cladribine Tablets, this study primarily evaluated safety outcomes, and thus additional real-world data are needed to understand the long-term effects of Cladribine Tablets on key measures of disability progression and to address the knowledge gaps around treatment patterns of patients with MS in a clinical setting.

2.3 Benefit/Risk Assessment

The primary aim of this study is to generate evidence regarding long-term disability progression and treatment sequencing following Cladribine Tablet treatment. 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.

As this study does not involve administration of any investigational medicinal product (IMP), there are minimal risks to the patients involved. Patients who come to the clinic will be asked to provide an optional blood sample for pharmacogenetics testing only if they consent to this additional sample and testing. 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.

Only a subset of study participants will participate in the MRI (without gadolinium) sub-study at Study Visit 2, and steps have been taken to minimize risk to patients participating in the MRI assessment by excluding study participants who are pregnant due to the unknown risks regarding rare fetal and childhood adverse event (AE) outcomes following exposure to MRI

during pregnancy. Any MRI scans will be performed according to a standard protocol detailed in a separate MRI user's manual, with appropriate safety precautions i.e. not including patients with MRI-incompatible metal in their body.

There are no restrictions or instructions for permitted or prohibited medicines for this study. Study participants will receive medicines according to their usual care under their treating physician. Once study participants have concluded their participation in this study, they will continue to be treated according to their usual practice and care and their usual care will not be affected by participation in this study.

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

3 Objectives and Endpoints

Data will be collected retrospectively and prospectively to evaluate the long-term outcomes, durability of effect, and real-world treatment patterns following treatment with Cladribine Tablets or placebo among patients with MS who were part of the parent studies. The objectives of this study are all exploratory and for hypothesis generating purposes.

Exploratory Objectives	Endpoints (Outcome Measures)
Primary	
To evaluate long-term mobility after treatment with an investigational medicinal product (IMP); Cladribine (Tablets or placebo) as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Proportion of study participants using a wheelchair (defined as unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day) the majority of the time in the 3 months prior to Study Visit 1 or participants are bedridden any time prior to Study Visit 1 determined via: 1) Expanded Disability Status Score (EDSS) score of 7.0 or higher, or 2) Alternative clinical description data in medical records
Secondary	
To assess the long-term disability status after treatment with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Proportion of study participants with EDSS of 6.0 or higher as determined by EDSS documentation or alternative clinical description in medical records after last IMP from parent study.
To evaluate differences in clinical characteristics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Clinical characteristics[a] at Study Visit 1 of long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to those of other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.

Exploratory Objectives	Endpoints (Outcome Measures)
To evaluate differences in magnetic resonance imaging (MRI) characteristics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	MRI characteristics[c] at Study Visit 2 of long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to those of other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.
Tertiary	
To assess the real-world treatment patterns in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Time, type, and reason for first sequential treatment after first course[b] of IMP, type of second sequential treatment, as well as the frequency of routine clinical monitoring and disease activity status as well as clinical and demographic characteristics[a] available for the CLARITY/CLARITY-EXT and ORACLE MS populations.

Exploratory Objectives	Endpoints (Outcome Measures)
To assess durability of clinical outcomes after treatment with IMP from Baseline (i.e. first dose[b] of IMP) to Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Tertiary endpoints to be evaluated via retrospective data collection from medical records or at Study Visit 1: • Proportion of study participants being bedridden[d] • Time from first dose[b] of IMP to first use of an ambulatory device[d] • Time from first dose[b] of IMP to first use of a wheelchair[d] • Annualized Relapse Rate (ARR) from time of first dose[b] of IMP to Study Visit 1, and by 2-year intervals • Time to conversion to Clinically Definite MS (CDMS) (For ORACLE MS study participants only) • Proportion of study participants diagnosed as Secondary Progressive MS (SPMS) without relapses in the 3 months prior to SPMS diagnosis • Proportion of study participants diagnosed as SPMS with relapses in the 3 months prior to SPMS diagnosis • Proportion of study participants diagnosed as Primary Progressive MS (PPMS) (For ORACLE MS study participants only)

Exploratory Objectives	Endpoints (Outcome Measures)
To assess impact on quality of life and cognitive outcomes after treatment with IMP during the period from the last clinical visit in the CLARITY/CLARITY-EXT/ORACLE MS clinical trials to Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Tertiary endpoints to be evaluated at Study Visit 1: • Change in EuroQoL-5 Dimension Questionnaire (3 level version) (EQ-5D-3L) • Change in cognition as measured by the following assessments (to be collected for ORACLE MS subjects only in countries where these instruments were used in the CLASSIC MS study): o The Brief Visuospatial Memory Test – Revised (BVMT-R) o Symbol Digit Modality Test (SDMT)
To assess durability of outcome on brain imaging after treatment with IMP from Baseline (i.e. the last MRI before first dose[b] of IMP; if feasible, by year) to within 3 months after Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	ORACLE MS, CLARITY and CLARITY-EXT study participants from selected sites will be invited to participate in a follow-up study visit (Study Visit 2) to take place within 3 months (maximum 4 weeks from Study Visit 1 after last patient enrolled) following Study Visit 1, for evaluation of the following: Change in MRI assessment from Baseline (i.e. the last MRI before first dose[b] of IMP) to Study Visit 2 in: • Total volume of T2 lesions • Total number of T2 lesions • Number of hypointense lesions on T1-spin echo MRI • Volume of hypointense lesions on T1-spin echo MRI • Brain volume or surrogate (in cases where brain volume is not possible to assess for technical reasons, then 3rd ventricle diameter may be evaluated) • Ventricular volume

Exploratory Objectives	Endpoints (Outcome Measures)
To determine whether the high-disease activity (HDA) patients from the CLARITY/CLARITY-EXT clinical trials are more likely to be the long-term responders.	Comparison of the responder rate in HDA patients[e] versus the responder rate in non-HDA patients from the CLARITY/CLARITY-EXT population.
To evaluate differences in genetics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Correlation of genetic variations with long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.

ARR=Annualized Relapse Rate, BVMT-R=Brief Visuospatial Memory Test Revised, CDMS=Clinically Definite Multiple Sclerosis, EDSS=Expanded Disability Status Scale, EQ-5D=EuroQoL-5 Dimension, HDA=High-disease activity, IMP=Investigational Medicinal Product, MRI=Magnetic Resonance Imaging, MS=Multiple Sclerosis, PPMS=Primary Progressive MS, RRMS=Relapsing-Remitting Multiple Sclerosis, SDMT=Symbol Digit Modalities Test, SPMS=Secondary Progressive Multiple Sclerosis.

[a] Specific clinical and demographic characteristics may include gender, age, race, ethnicity, education, disease duration, years previous disease modifying treatment (before start of CLARITY/CLARITY-EXT/ORACLE MS) and disease classification (RRMS or SPMS).

[b] One dose is equivalent to one tablet. One course of IMP is defined as 1 year of treatment with IMP (2 treatment cycles [weeks]). A treatment cycle is defined as daily administration of IMP given consecutively over 4-5 days during a 28-day period. One treatment week is equivalent to 1 treatment cycle.

[c] Total volume of T2 lesions; Total number of T2 lesions; Number of hypointense lesions on T1-spin echo MRI; Brain volume or surrogate; Ventricular volume.

[d] Mobility endpoints may be determined via EDSS scores (if available) or corresponding clinical descriptions in medical records.

[e] 1. Patients with ≥2 relapses during the year prior to parent study entry, regardless of prior disease modifying drugs (DMD) use; 2. Patients with ≥1 relapse in the previous year and ≥1 T1 Gd+ lesions or ≥9 T2 lesions, while on therapy with other DMDs.

4 Study Design

4.1 Overall Design

This Phase IV, low-interventional, multicenter, ambispective study will involve the evaluation of medical records of study participants treated with Cladribine Tablets or placebo (IMP) in the previously conducted parent studies. Long-term retrospective data will be collected through evaluation of medical charts/records, and additional prospective data will be

collected. No IMP will be administered as part of this study. An interim analysis is planned when data from approximately 100 patients are collected (see Section 9 for further details on analyses).

This study will collect data from study participants with MS who participated in the CLARITY/CLARITY-EXT clinical trial(s) and who received ≥ 1 course of IMP, or study participants with their FCDE who were randomized in the ORACLE MS study and received ≥ 1 course of IMP.

An overall Study Schema is depicted in Section 1.2. Additionally, details of the different timelines according to subject relapse status at the time of screening, and for participants completing the study remotely are presented in Section 1.2, and a detailed SoA is provided in Section 1.3.

Participants are invited to up to 3 clinic visits for this study. The first visit is the Screening Visit. The following screening activities may be administered by telephone if the patient is unable and/or not willing to attend clinic for the visit, depending on approval by Ethics Committees (ECs), Institutional Review Boards (IRBs), and/or local regulations: Informed consent (for patients participating in retrospective data collection only, local requirements for patient consent will be observed, which may include informed consent form [ICF] waiver), sociodemographic and clinical characteristics, medical and disease history, and study inclusion/exclusion determination.

Retrospective data for deceased or lost to follow-up patients will be collected in case an ICF waiver is granted, or proxy/caregiver/legal representative consent is obtained, depending on approval by ECs, IRBs, and/or local regulations.

The second visit is Study Visit 1, which could be combined with the Screening Visit. At this visit retrospective data (from medical chart review) and current data will be collected. For patients who are able to attend the visit at the clinic data on a physical assessment, Expanded Disability Status Scale (EDSS), Patient-Reported Outcomes (PROs), cognitive assessments, AEs and concomitant medications will be collected. For all patients the following retrospective data will be collected: EDSS, Secondary Progressive MS (SPMS) conversion, details of subsequent DMDs, including physician questions on treatment decisions, date of first use of an ambulatory device or wheelchair, date of first time bedridden and relapse history from end of parent study to Study Visit 1. In ORACLE MS patients, CDMS conversion and PPMS diagnosis will be assessed as well. An optional blood sample for pharmacogenetic testing will be taken from patients who consent to the optional sampling at the clinic and who are seen at a site with available capabilities to store and ship these samples. Patients will also have the opportunity to provide pharmacogenetic samples after Study Visit 1 and up to 6 months from Screening (unless last patient enrolment has occurred, in which case the sample can only be collected at Study Visit 1).

For patients from whom in-person EDSS at clinic visit was not planned to be collected, a telephone EDSS questionnaire will be administered. Attempts should be made to administer the telephone EDSS within 14 days after informed consent was received for patients not attending the clinic visit.

Study data will be supplemented with information from the past clinical trial(s), which will be integrated for milestones such as interim analyses and, if needed, on a regular basis. It is the Sponsor, not the site, that is responsible for obtaining the information from the past clinical trial(s) study databases. However, the sites will be requested to provide some patient identifiers (e.g. patient number, parent study patient participated in, year of birth and gender) to match data being collected with previous data sets.

The third potential clinic visit is Study Visit 2, which involves an MRI scan without gadolinium in approximately 150 patients who are willing to participate in this MRI sub-study. The sites that participate in the MRI sub-study will be selected primarily based on their technical capabilities to perform the required MRI assessments and the availability of the original MRI machine from the parent studies. The patients at these sites will be selected based on being able to fulfill the eligibility criteria (see Section 6.5.4.2), including the availability/consent of the patient to perform a new MRI and the provision of a urine pregnancy test within a week prior to the MRI assessment (for female patients of childbearing age). A serum pregnancy test is also acceptable if available as per standard of care (SOC). Verbal reporting of pregnancy status by the female patient is not acceptable. AEs and concomitant medications will also be reviewed and recorded during this visit. For patients who are not experiencing relapse at the time of screening, the duration between Screening Visit to Study Visit 1 is no more than 2 weeks, including for patients who are participating remotely and who are completing a telephone EDSS assessment only. For patients experiencing relapse, the duration between Screening and Study Visit 1 is between 4 weeks and 3 months. For patients selected to participate in the MRI sub-study, an additional visit will be required that will occur within a maximum of 3 months of Study Visit 1 (maximum 4 weeks from Study Visit 1 if last patient recruitment has occurred), and these patients' total study duration will likely be no more than 3.5 months if the patient was not experiencing relapse at Screening, or up to 6 months maximum in the case of relapse. For patients providing samples for pharmacogenetic testing, the time window for sample collection is up to a maximum of 6 months from Screening (unless last patient enrolled has occurred, in which case the testing must occur at Study Visit 1). Sites will be asked to enter any retrospective data into the electronic case report form (eCRF) for this study within 12 weeks of enrolling the patient. Participants who are eligible will be given the option of completing the screening, Study Visit 1, and 2 (where facilities for MRI are available) on the same day if prefer to do so and meet the eligibility criteria on that day (e.g. abstention from alcohol or cannabinoid products in the preceding 24 hours). Participants who are undergoing relapse or suspected relapse at the time of screening will be invited for Study Visit 1 after a stabilization period determined through consultation with the medical monitor.

The study aims to enroll patients from approximately Q3 2019 to Q1 2021. Last Patient Last Visit is expected in Q1 2021 (see Section 4.4 End of Study Definition).

Patient selection bias will be addressed through specific statistical methods (see Section 9 for further details on statistical considerations). Site selection bias will be addressed by robust site feasibility open to all sites that participated in the parent studies.

4.2 Scientific Rationale for Study Design

The purpose of this study is to explore the long-term outcomes, durability of effect, and real-world treatment patterns in patients previously participating in the parent studies. This exploratory Phase IV study includes retrospective and prospective assessments. It will involve the collection of long-term retrospective data through abstraction of medical charts/records. For patients participating in the prospective assessment of the study, additional data will be collected at Study Visit 1 and patients will be asked for an optional blood sample. For a subset of patients, an MRI assessment will be performed at Study Visit 2, which will occur within a maximum of 3 months after completing Study Visit 1 (maximum 4 weeks from Visit 1 if last patient recruitment has occurred). No IMP will be administered as part of this study.

The primary objective of this study is to evaluate long-term mobility after treatment with Cladribine Tablets or placebo in the parent studies. This will be evaluated by the primary endpoint, the proportion of study participants using a wheelchair (defined as unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day) the majority of the time in the 3 months prior to Study Visit 1 or participants are bedridden any time prior to Study Visit 1, determined via EDSS score of 7.0 or higher, or alternative clinical description data in medical records. This primary endpoint was selected as a reliable and valid measure of long-term mobility following treatment with IMP in the parent studies. This endpoint was agreed upon by the Steering Committee members as one that is practical for this ambispective study design, as use of a wheelchair or being bedridden is a disability milestone for patients with MS and will likely be recorded in medical charts, either as a clinical description or via an EDSS score of 7.0 or higher. This endpoint is also practical to evaluate at Study Visit 1, thus maximizing the amount of data that can be collected for the primary endpoint in this study.

The secondary objective is the comparison of clinical characteristics between long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose of IMP) compared to those who started on alternate therapy less than 4 years following their last dose of IMP for the combined parent study populations. This secondary objective helps to fill an important data gap, which is understanding treatment sequencing following Cladribine Tablets and specifically understanding if there are differences in clinical characteristics (gender, age/year of birth, race, ethnicity, education, employment status, disease duration [years], current disease modifying treatment, time since last relapse [months], and disease classification [RRMS or SPMS]) between study participants who did and did not start on an alternative therapy within 4 years of their last dose of IMP in the parent studies.

The study will enroll study participants with MS who participated in the CLARITY/CLARITY-EXT clinical trials and who received ≥ 1 course of IMP (Cladribine Tablets or placebo), or with their FCDE who were randomized in the ORACLE MS study and received ≥ 1 course of IMP (Cladribine Tablets or placebo). Data collection for this study is based on study participants recruited into previously conducted clinical trials which had

defined inclusion and exclusion criteria. Therefore, the chosen inclusion criteria (Section 5.1) aim to be as inclusive as possible to maximize the number of study participants from the parent studies who can be enrolled, while allowing for the patient or their proxy/caregiver/legal representative (in cases where an ICF waiver will not apply) to consent to allow the collection of retrospective data and/or prospective data in order to maximize the data that can be collected in this exploratory study. The chosen exclusion criteria (Section 5.2) will protect the safety of study participants by excluding particularly vulnerable individuals.

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 visit and/or the last scheduled procedure shown in Section 1.3 (Schedule of Activities).

The end of the study is defined as the date of the last patient's last visit. For study participants taking part in the main study only (i.e. for participants not participating in the MRI sub-study), a participant has completed the study if he/she has completed all study parts, including the Study Visit 1, which will be the last patient's last visit collected for the study. For those also taking part in the MRI sub-study, the Study Visit 2 will be the last study participant's last visit.

A clinical study protocol may not be considered closed as long as:

- Visits specified by the protocol are still taking place, or
- Procedures according to the protocol are still being undertaken in any patient.

During study participation and once patients have concluded their participation in this study, they will continue to be treated as part of their usual practice and care.

5 Study Population

The study population will be patients with MS randomized in the CLARITY or CLARITY-EXT study who have received ≥ 1 course of IMP (Cladribine Tablets or placebo) or patients with their FCDE randomized in the ORACLE MS study who have received ≥ 1 course of IMP.

The criteria in Sections 5.1 (Inclusion Criteria) and 5.2 (Exclusion Criteria) 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 should be taken into consideration 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 proxy/caregiver/legal representative has provided written informed consent, or an ICF waiver is in place, if permitted by local regulation and approved by the relevant EC/IRB.

5.1 Inclusion Criteria

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

1. Patients with MS randomized in CLARITY/CLARITY-EXT clinical trial(s) who have received ≥ 1 course of IMP (Cladribine Tablets or placebo).

   or

   Patients with their FCDE randomized in ORACLE MS clinical trial who have received ≥ 1 course of IMP (Cladribine Tablets or placebo).

Informed Consent

2. Can give signed informed consent, as indicated in Appendix 2 (Study Governance), which includes compliance with the requirements and restrictions listed in the ICF and this protocol. Data will be collected from the medical records of deceased or lost to follow-up patients if consent is obtained by participant's proxy/caregiver/legal representative or if an ICF waiver is in place, if permitted by local regulation and approved by the relevant EC/IRB.

5.2 Exclusion Criteria

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

Medical Conditions

Any condition, including any uncontrolled disease state other than MS, that in the Investigator's opinion, constitutes an inappropriate risk or a contraindication for participation in the study or that could interfere with the study objectives, conduct, or evaluation. If a patient is experiencing a confirmed or suspected relapse at the time of screening, the Medical Monitor is to be consulted to agree on a stabilization period (estimated to be between 4 weeks and 3 months) before Study Visit 1.

For specific exclusion criteria for the MRI sub-study please see Section 6.5.4.2 (MRI Sub-Study).

5.3 Lifestyle Considerations

5.3.1 Meals and Dietary Restrictions

Not applicable. This study does not have any meal/dietary restrictions to specify.

5.3.2 Caffeine, Alcohol, Tobacco, and Cannabinoid-containing Products

Twenty-four hours prior to Study Visits 1 and Study Visit 2, when cognitive assessments or MRI procedures may be performed, participants will abstain from alcohol and cannabinoid-containing products.

5.3.3 Activity

Not applicable. This study does not have any restrictions on participant activity level to specify.

5.4 Screen Failures

Individuals who do not meet the criteria for participation in this study (screen failure) may not be rescreened. Patients with confirmed or suspected relapses can remain in the study, and Study Visit 1 will be postponed until the patient has stabilized.

6 Study Intervention(s)

Study intervention is any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant per the study protocol.

6.1 Study Intervention(s) Administration

This study does not involve administration of any IMP. Participants enrolled will have participated in CLARITY/CLARITY-EXT and ORACLE MS clinical trials, where they received Cladribine Tablets or placebo according to those study protocols.

6.1.1 Medical Device(s) Use

Not Applicable. No medical devices are provided for use in this study.

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

Not Applicable.

6.3 Measures to Minimize Bias: Study Intervention Assignment and Blinding

6.3.1 Study Intervention Assignment

Not Applicable.

6.3.2 Blinding

Not Applicable.

6.3.3 Emergency Unblinding

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.

The use of concomitant medications and therapies is not controlled as part of this study. The first sequential disease modifying MS therapy that was taken following treatment with Cladribine Tablets, and the categorization of the second sequential treatment following Cladribine Tablets (categorized by platform injectable therapies, monoclonal antibody disease modifying treatments, oral disease modifying treatments, other, and unknown treatments) will be assessed through retrospective review of the patient's medical records and captured as part of the CRF.

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

6.5.1 Rescue Medicine

There are no restrictions or instructions for rescue medicines for participants in this study. Participants will receive medicines as part of their usual care by their treating physician.

6.5.2 Permitted Medicines

There are no restrictions or instructions for permitted medicines for participants in this study. Participants will receive medicines as part of their usual care under their treating physician.

6.5.3 Prohibited Medicines

There are no prohibited medicines in this study. Study participants will receive medicines as part of their usual care under their treating physician.

6.5.4 Other Interventions

6.5.4.1 Optional Blood Sampling for Pharmacogenetics Testing

Patients willing to consent to provide an optional blood sample and who are seen at a site with available capabilities to store and ship samples will have a blood draw taken at Study Visit 1 for pharmacogenetics testing.

6.5.4.2 MRI Sub-Study

The population to be included in the MRI sub-study will be based on the availability/consent of the patient to perform a new MRI, availability of the original machine and other technical site capabilities that will be defined following assessment of site feasibility to conduct the MRI sub-study.

For study participants at selected sites where MRI assessments will be conducted, the following exclusion criteria will apply to the MRI assessment only:[1]

a. Female study participants who are pregnant[2]
b. Patients were administered Cladribine Tablets through prescription or as part of another study within 6 month period before enrolment in the MRI Sub-study (i.e. patients participating in a clinical trial or observational study within the 6 month period before enrolment in the MRI Sub-study, but do not receive Cladribine Tablets as part of these studies, are allowed to participate in the sub-study).

Patients willing to provide their consent to participate in the MRI sub-study and who do not meet any of the above exclusion criteria will have an MRI without gadolinium taken. Any MRI scan will be performed according to a standard protocol detailed in a separate MRI scan user's manual. A central neuroradiology center will perform the analysis of all MRI scans. As with other laboratory tests and clinical measures, strict adherence to the MRI scanning protocol and prompt handling of the scans is essential in obtaining a meaningful result. A urine pregnancy test will be conducted in female patients of childbearing potential participating in the MRI sub-study within a week prior to the MRI assessment. A serum pregnancy test is also acceptable if available as per SOC. Verbal reporting of pregnancy status by the female patient is not acceptable. For pregnant female patients the MRI visit may be rescheduled for a later date (within the timeframes specified in Section 4.1) following pregnancy outcome.

Prior to patient assessment, each study site will be asked to send a 'test' or 'dry-run' scan to assess image quality and shipment procedures, to evaluate the accessibility of the electronic data carrier, and to assess the ability to correctly reposition patients to get comparable brain images. Only upon final approval of this test scan, sites will be allowed to begin assessing patients. Once patients are enrolled, the quality of the scans will be assessed as soon as possible, as part of an ongoing quality control procedure. Investigators will be informed about the acceptance of scans and the need for scans to be repeated due to protocol deviations.

[1] If patient is not eligible for MRI, MRI will not be performed but clinical data for other objectives may be collected.
[2] Due to unknown risks regarding rare foetal and childhood adverse event outcomes following exposure to MRI during pregnancy (Ray, 2016), MRI procedures will not be performed for female patients who are pregnant, but may be scheduled for a later follow up date following pregnancy outcome.

6.6 Dose Selection and Modification

Not Applicable.

6.7 Study Intervention After the End of the Study

Throughout the duration of the study, participants will continue to receive their SOC treatment. Once participants have concluded their participation in this study, they will continue to be treated as part of their usual practice and care.

6.8 Special Precautions

Subject to the applicable local laws and regulations, patients who cannot participate or complete the SoA due to cognitive impairment or relapsing episode and are thus not able to give informed consent will be given the opportunity to participate by their proxy/caregiver/legal representative providing consent on their behalf.

Study visits for participants who are relapsing can be postponed until it is appropriate for them to complete study visit assessments. The decision to postpone the study visit will be made at the discretion of the physician based on the ability of the patient to attend the clinic and complete the assessments without causing discomfort or harm to the patient.

6.9 Management of Adverse Events of Interest

Adverse events of special interest (AESIs) for this study as defined in the SmPC should be considered as a medically significant AE and reported to the Sponsor using a Serious Adverse Event (SAE) Report Form with all related information.

Three main categories of AEs were defined as AESI:

- Severe (≥ Grade 3) lymphopenia: Lymphopenia is an expected event based on the mechanism of action of cladribine, an adenosine deaminase-resistant analog of deoxyadenosine, that after conversion to its active triphosphate form (2-Cd-ATP), decreases peripheral lymphocyte counts; grading should be performed according Common Terminology Criteria for Adverse Events where Grade 3 is defined as $< 500/mm^3$- $200/mm^3$.

- Infections: Defects in cell-mediated immunity and immunosuppressive conditions may predispose patients to infectious diseases.

- Malignancies: Immunodeficiency could lead to an increased risk for the development of malignancies; however, this is generally seen where immunosuppression is profound and long-lasting. Malignancy cases have been reported in MS patients treated with other DMDs. In view of these considerations the potential risk of malignancy for Cladribine Tablets has been thoroughly evaluated.

7 Discontinuation of Study Intervention and Participant Discontinuation/Withdrawal

7.1 Discontinuation of Study Intervention

Not Applicable.

7.1.1 Temporary Discontinuation

Not Applicable.

7.1.2 Rechallenge

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 (i.e., withdrawal of consent), and without giving a reason.
- Patients' proxy/caregiver/legal representative may withdraw consent at any time as well, without giving a reason.
- For the MRI sub-study, the participant may be withdrawn by the Investigator due to participation in another clinical study if the participant receives Cladribine Tablets in the other clinical study.
- The participant may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, or administrative reasons.
- The SoA specifies the data to collect at each follow-up visit, and any additional evaluations that need to be completed. These assessments are not mandatory, and patients can remain in the study if certain assessments (e.g. PROs) are not completed.
- Participants can withdraw consent for the optional pharmacogenetic testing any time; this does not preclude them from continuing in the study and complete other assessments.

The patient will be informed that any data collected from the signature of the informed consent until the point of withdrawal will be maintained and included in the analysis (pending review and approval by ECs, IRBs and/or local regulations and patient consent). The Investigator should make every attempt to clarify the level of withdrawal: e.g., if the participant can still be contacted by phone for checking his/her status (e.g., alive or not). In case of withdrawal from the study, the appropriate CRF section must be completed.

If a participant withdraws consent from the optional pharmacogenetic testing before the samples have been analyzed, the participant's samples will be destroyed without being analyzed. In addition, data collected will be excluded from the analysis. If a participant withdraws from the pharmacogenetic testing after the participant's sample has been analyzed, any information learned from the analysis will remain part of the study database and may not be removed.

Participants or their proxy/caregiver/legal representative will be informed that they have the right to withdraw from the study at any time, without prejudice to their medical care, and that they are not obliged to state their reasons. Any withdrawal must be fully documented in the eCRF and source documents and should be followed up by the Investigator. The Investigator may withdraw a patient at any time if this is considered to be in the patient's best interest.

Participants who are discontinued/withdrawn from the study will not be replaced.

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 must be taken if a participant fails to return to the clinic for a required study visit:

- The site must 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 must 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 should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8 Study Assessments and Procedures

- Study assessments and procedures and their timing are summarized in Section 1.3 (Schedule of Activities).
- **No** protocol waivers or exemptions are allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue the study.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must 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 or before entering data in the study electronic data capture (EDC) system, the Investigator will confirm that the participant or the participant's proxy/caregiver/legal representative has provided informed consent. Data will be collected from the medical records of deceased or lost to follow-up patients if consent

is obtained by participant's proxy/caregiver/legal representative or an ICF waiver is in place, if permitted by local regulation and approved by the relevant EC/IRB.

- Procedures conducted as part of the participant's routine medical care (e.g., pregnancy test for MRI sub-study) 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 SoA.

8.1 Efficacy Assessments and Procedures

A detailed schedule of study procedures/assessments is provided in the SoA (Section 1.3).

During the Screening Visit, the patient or their proxy/caregiver/legal representative will be informed of the study objectives and overall requirements, and informed consent will be obtained prior to any study specific assessments, unless an ICF waiver is in place (see Appendix 2 Study Governance for details on informed consent process). The site will also confirm that patients meet the Inclusion/Exclusion Criteria. During this visit, a complete Screening Evaluation will be performed, which will capture sociodemographic and clinical characteristics (including gender, age/year of birth, race and ethnicity where permitted, employment status and education level attained), medical history, and disease history (including classification of disease and diagnosis date). These screening activities may be administered by telephone if the patient is unable to attend the clinic for study visits, dependent on approval by ECs, IRBs, and/or local regulations. For patients participating only in retrospective data collection, local requirements for patient consent will be observed, which may include informed consent waiver.

PRO questionnaires, followed by cognition assessments (for ORACLE MS patients only), should be performed prior to any other assessments.

For patients participating in the MRI assessment, attempts should be made to perform Study Visit 2 within 3 months (maximum) after completing Study Visit 1 (maximum 4 weeks from Study Visit 1 after the last patient has been recruited). A urine pregnancy test will be performed within a week prior to the MRI assessment in female patients of childbearing potential. A serum pregnancy test is also acceptable if available as per SOC. Verbal reporting of pregnancy status by the patient is not acceptable. The Investigator will ensure that the patient or the patient's proxy/caregiver/legal representative has provided specific informed consent to participate in MRI assessments.

8.1.1 Clinical Endpoints

8.1.1.1 Expanded Disability Status Scale (EDSS)

The EDSS is a neurological assessment that will be used to assess the long-term disability progression following treatment with IMP in the parent studies (Appendix 5Expanded Disability Status Scale (EDSS)). EDSS is a scale from 0-10 that evaluates a person with MS's disability/neurologic function level with 6 being the critical point at which a patient requires ambulatory assistance. The primary endpoint of proportion of study participants using a wheelchair (defined as unable to walk beyond approximately 5 meters even with aid,

essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day) the majority of the time in the 3 months prior to Study Visit 1 or participants are bedridden any time prior to Study Visit 1 determined via an EDSS score of 7.0 or higher (if available), or alternative clinical description data in medical records. The secondary endpoint will be determined as the proportion of study participants with EDSS of 6.0 or higher by EDSS documentation or alternative clinical description in medical records after last IMP from parent study.

Sustained disease progression is important because transient increases in the EDSS may also be due to relapses, which reflect disease activity rather than disease progression (Healy, 2013); an EDSS measurement taken at a single point in time may be subject to measurement error (Goodkin, 1992). As such, confirmation of sustained EDSS score is needed to mitigate against measurement error and EDSS fluctuation (Kalincik, 2015).

Furthermore, while EDSS scores at any timepoint, regardless of their relationship to relapses, may serve as evidence of EDSS progression, it is generally recommended that only EDSS scores that are recorded more than 30 days from the onset of a preceding relapse be used in order to confirm progression events (Kalincik, 2015). As such, Investigators in this study will be instructed to exclude any EDSS score recorded within 30 days of a previous relapse.

The in-person EDSS will be completed by the evaluating physician for those study participants who can come to the clinic for Study Visit 1. Alternatively, a telephone EDSS score can be determined by telephone interview in which trained clinical site staff member to administer the EDSS telephone questionnaire (Lechner-Scott, 2003). The telephone EDSS will be collected only from patients not attending clinic visits, and will be collected within 14 days of obtaining informed consent. Only one mode of the collection (in-person during a clinic visit, or by telephone) is required per patient. Retrospective EDSS scores will be ascertained from medical records for the time period between end of parent study to Study Visit 1 (when available).

Reasons for inability to come to the clinic for Study Visit 1 may include travel/migration, or limited mobility (bedridden), or clinical site restrictions due to COVID-19. In addition, patients may not want to come to the clinic for Study Visit 1 due to a lack of interest..

8.1.1.2 EDSS Confidence Scale

For each EDSS score that is obtained retrospectively from medical charts and at the time of Study Visit 1, the evaluating physician will be asked to complete the EDSS Confidence Scale which is a single question indicating their confidence in that score's accuracy. This will be based on a non-validated 4-point Likert scale where 0 = not at all confident and 3 = highly confident.

8.1.1.3 Bedridden Status

A patient's status as being bedridden will be determined by EDSS scores of 8.0 or higher ("essentially restricted to bed or chair or perambulated in wheelchair but may be out of bed itself much of the day"), if available, or by clinical descriptions in medical records.

8.1.1.4 Subsequent Disease Modifying Drugs and Treatment Decisions

Details of subsequent DMDs, including physician questions on treatment decisions will be captured in the eCRF, based on chart review to determine the time, type, and reason for the first sequential treatment after the first course of Cladribine Tablets and the categorization of the second sequential treatment (categorized by platform injectable therapies, monoclonal antibody disease modifying treatments, oral disease modifying treatments, other, and unknown treatments).

8.1.1.5 First Use of Ambulatory Device

The date of first use of ambulatory device will be determined through retrospective chart review, based on an EDSS score of 6.0 or higher (score of 6.0 is defined as "intermittent or unilateral constant assistance [cane, crutch, brace] required to walk about 100 meters with or without resting") or clinical descriptions if EDSS scores are not available.

8.1.1.6 First Use of Wheelchair

The date of first use of a wheelchair will be determined through retrospective chart review, based on an EDSS score of 7.0 or higher (score of 7.0 is defined as unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day) or clinical descriptions if EDSS scores are not available.

8.1.1.7 Relapse Count

The following information on relapses will be recorded on the relapse module of the eCRF, if available: the number of relapses from end of parent study to Study Visit 1; relapse onset date and stabilization/resolution date; estimated relapse duration; maximal EDSS at time of relapse (if known); major systems affected; treatment required for relapse; patient hospitalization for relapse; outcome of relapse (i.e. increase in disability). A relapse will be defined as patient-reported symptoms and objectively observed signs typical of an acute inflammatory demyelinating event in the CNS, developing acutely or sub-acutely, with duration of at least 24 hours, in the absence of fever or infection (Thompson, 2018).

8.1.1.8 Conversion to Clinically Definite Multiple Sclerosis (ORACLE MS Participants Only)

Conversion to CDMS will be determined according to the McDonald 2017 criteria (Thompson, 2018; Table 2). For more details please see Appendix 6 2017 Mc Donald Criteria (From Thompson, 2018)).

Table 2 **The 2017 McDonald criteria for diagnosis of Multiple Sclerosis in patients with an attack at onset**

Clinical Presentation	Additional Data Needed to Make MS Diagnosis
• ≥2 attacks and objective clinical evidence of ≥2 lesions • ≥2 attacks and objective clinical evidence of 1 lesion with historical evidence of prior attack involving lesion in different location	None. Dissemination in space (DIS) and dissemination in time (DIT) have been met.
• ≥2 attacks and objective clinical evidence of 1 lesion	One of these criteria: • DIS: additional clinical attack implicating different CNS site • DIS: ≥1 symptomatic or asymptomatic MS-typical T2 lesions in ≥2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial or spinal cord
• 1 attack and objective clinical evidence of ≥2 lesions	One of these criteria: • DIT: additional clinical attack • DIT: simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions • DIT: new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) • Cerebrospinal fluid (CSF)-specific (i.e. not in serum) oligoclonal bands
• 1 attack and objective clinical evidence of 1 lesion	One of these criteria: • DIS: additional attack implicating different CNS site • DIS: ≥1 MS-typical symptomatic or asymptomatic T2 lesions in ≥2 areas of CNS: periventricular, juxtacortical/cortical, infratentorial or spinal cord AND One of these criteria: • DIT: additional clinical attack • DIT: simultaneous presence of both enhancing and non-enhancing symptomatic or asymptomatic MS-typical MRI lesions • DIT: new T2 or enhancing MRI lesion compared to baseline scan (without regard to timing of baseline scan) • CSF-specific (i.e. not in serum) oligoclonal bands

8.1.1.9 Diagnosis of Secondary Progressive Multiple Sclerosis Without Relapses

SPMS without relapses will be defined as follows (Lublin, 2014; Kappos, 2018):

- Documented moderate-to-advanced disability indicated by EDSS score of 3.0–6.5 at time of diagnosis of SPMS
- A history of RMS diagnosis
- Documented at least 6 months sustained EDSS progression based on clinical judgment
- Without evidence of relapses in the 3 months before SPMS diagnosis

Conversion to SPMS will be ascertained by the evaluating physician retrospectively from medical records or determined at Study Visit 1 (for study participants who may have converted to SPMS between last regular clinic visit and Study Visit 1).

8.1.1.10 Diagnosis of Secondary Progressive Multiple Sclerosis With Relapses

SPMS with relapses will be defined as follows (Lublin, 2014; Kappos, 2018):

- Documented moderate-to-advanced disability indicated by EDSS score of 3.0–6.5 at time of diagnosis of SPMS
- A history of RMS diagnosis
- Documented at least 6 months sustained EDSS progression based on clinical judgment
- With evidence of relapses in the 3 months before SPMS diagnosis

Conversion to SPMS will be ascertained by the evaluating physician retrospectively from medical records or determined at Study Visit 1 (for study participants who may have converted to SPMS between last regular clinic visit and Study Visit 1).

8.1.1.11 Diagnosis of Primary Progressive Multiple Sclerosis (ORACLE MS Participants Only)

As per the McDonald 2017 criteria (Thompson, 2018), PPMS can be diagnosed in patients with:

- One year of disability progression (retrospectively or prospectively determined) independent of clinical relapse

Plus 2 of the following criteria:

- One or more T2-hyperintense lesions[3] characteristic of multiple sclerosis in one or more of the following brain regions: periventricular, cortical or juxtacortical, or infratentorial
- Two or more T2-hyperintense lesions[3] in the spinal cord
- Presence of cerebrospinal fluid (CSF) -specific oligoclonal bands

8.1.1.12 Cognition Endpoints (ORACLE MS Participants Only)

Cognition measures to be administered at Study Visit 1 are as follows:

- The Brief Visuospatial Memory Test – Revised (BVMT-R)
- Symbol Digit Modality Test (SDMT)

Note that the BVMT-R and SDMT assessments are to be collected for ORACLE MS subjects only in countries where these instruments were used in the CLASSIC MS study.

8.1.1.13 Brain Imaging

A subset of study participants from the parent studies will be invited to participate in a follow-up study visit (Study Visit 2) for an MRI assessment without gadolinium, to evaluate the following parameters associated with chronic disease activity in MS patients:

- Total volume of T2 lesions
- Total number of T2 lesions
- Number of hypointense lesions on T1-spin echo MRI
- Volume of hypointense lesions on T1-spin echo MRI
- Brain volume or surrogate (In cases where brain volume is not possible to assess for technical reasons, then 3rd ventricle diameter may be evaluated)
- Ventricular volume

8.1.2 Other Assessments

8.1.2.1 Patient-reported Outcomes/Quality of Life: EQ-5D-3L

The 3-level version of the EuroQoL-5 Dimension questionnaire (EQ-5D-3L) will be administered at Study Visit 1. The EQ-5D-3L is a validated, self-administered, generic, utility instrument that includes 5 single-item dimensions: mobility, self-care, usual activities,

[3] Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required.

pain/discomfort, and anxiety/depression (EuroQoL Group, 1990). Study participants must choose between 3 levels of difficulty in accomplishing tasks in each dimension. The questionnaire also contains a Visual Analog Scale for the study participants to rate their current health state from 0 (worst imaginable health state) to 100 (best imaginable health state).

8.1.2.2 Frequency of Stable Patient Monitoring Questions

Each evaluating physician at the clinical sites will be asked to complete questions assessing how frequently the study patients with MS are monitored and evaluated at their site in regular clinical practice. These questions ask about frequency of follow-up visits and follow-up MRI assessments if the study patients with MS are considered stable.

8.2 Safety Assessments and Procedures

The safety profile of this study's interventions will be assessed through the recording, reporting and analysis of medical conditions, AEs, physical examination findings, and vital signs as specified in the SoA (Section 1.3). A comprehensive assessment of any potential AE experienced by each participant will be conducted starting when the participants give informed consent and throughout the study. The Investigator will report any AE, whether observed by the Investigator or reported by the participant; the reporting period is specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information).

All clinically significant abnormalities occurring before signature of informed consent should be recorded in the Medical History section and/or Disease History; all abnormalities occurring or worsening after signature of informed consent should be recorded in the AE section unless otherwise stated by the protocol.

There are no specific safety endpoints included in this study.

8.2.1 Physical Examinations

- A complete physical examination will include, at a minimum, assessments of the Cardiovascular, Respiratory, Gastrointestinal and Neurological systems. Height and weight will also be measured and recorded.
- A brief physical examination will include, at a minimum, assessments of the skin, lungs, cardiovascular system, and abdomen (liver and spleen).
- Investigators should pay special attention to clinical signs related to previous serious illnesses.

8.2.2 Vital Signs

Vital signs will be assessed and interpreted as per SOC.

- Oral temperature, pulse rate, respiratory rate, and blood pressure will be assessed.
- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.

- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (e.g., television, cell phones).
- Vital signs will be measured in a semi-supine position after 5 minutes rest and will include temperature, systolic and diastolic blood pressure, and pulse and respiratory rate. Three readings of blood pressure and pulse will be taken. The first reading should be rejected. The second and third readings should be averaged to give the measurement to be recorded in the CRF.

8.2.3 Electrocardiograms

Not Applicable.

8.2.4 Clinical Safety Laboratory Assessments

Not Applicable.

8.2.5 Suicidal Risk Monitoring

Not Applicable.

8.3 Adverse Events and Serious Adverse Events

The definitions of an AE and a SAE are in Appendix 3 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting).

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

The AE reporting period for safety surveillance begins when the participant is initially included in the study (i.e. date of first signature of informed consent) and continues until Study Visit 1 or, if applicable, Study Visit 2.

All SAEs will be collected and reported as indicated in Appendix 3 from the signing of the informed consent form until study Visit 1 or, if applicable, Study Visit 2. Beyond this reporting period if investigator learns of any SAE at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator will promptly notify the Sponsor.

Please note, in addition to any AE/SAE which occurs after informed consent, any adverse drug reaction (ADR) that occurred after the End of Trial Visit in the parent study and is assessed as related to Cladribine Tablets by the Investigator must be recorded in the eCRF as well.

The method of recording, evaluating, and assessing causality of AEs (including SAEs) and the procedures for completing and transmitting SAE reports are in Appendix 3.

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. During the reporting period, any unfavorable changes in the participant's condition will be recorded as AEs, regardless if reported by the participant or their caregiver/legal representative or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined above) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported using the appropriate Report Form as specified in Appendix 3.

Due to the interventional nature of the MRI examination that is done specifically for the purpose of this study, the study specific procedure of AEs and SAEs data collection and reporting will be followed. The Sponsor's responsibilities regarding safety reporting will be carried out in accordance to the European Directive 2001/20/EC and with the related detailed guidance documents.

8.3.3 Follow-up of Adverse Events and Serious Adverse Events

AEs are recorded and assessed continuously throughout the study, as specified in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information) and are assessed for their outcome at the patient's last visit (i.e. Study Visit 1 for patients not participating in the MRI sub-study or Study Visit 2 for patients participating in the MRI sub-study). All SAEs ongoing at the patient's last visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the participant is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed. Further information on follow-up procedures is given in Appendix 3 (Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reports).

8.3.4 Regulatory Reporting Requirements for Serious Adverse Events

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations.

The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving study participants to the Independent Ethics Committee (IEC)/IRB that approved the study.

In accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), the Sponsor/designee will inform the Investigator of findings that could adversely affect the safety of participants, impact the conduct of the study or alter the IEC's/IRB's approval/favorable opinion to continue the study. In line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and considered to be related to the administered product ("suspected unexpected serious

adverse reactions" or SUSARs). The Investigator should place copies of Safety Reports in the Investigator Site File. National regulations regarding Safety Report notifications to Investigators will be considered.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For studies covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related detailed guidance documents.

8.3.5 Pregnancy

All pregnancies of female participants occurring during the Adverse Event Reporting Period, defined in Section 8.3.1 (Time Period and Frequency for Collecting Adverse Event and Serious Adverse Event Information), must be recorded in the AE page/section of the CRF.

For female participants in the MRI sub-study with an estimated conception date during the safety surveillance period (Section 8.3.1), the Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted by the same process specified for SAE reporting in Appendix 3, section on Reporting Serious Adverse Events and AESIs. Investigators must actively follow up, document and report on the outcome of all these pregnancies (among MRI sub-study participants, as described above), even if the participants are withdrawn from the study. The Investigator must notify the Sponsor/designee of the outcomes of pregnancies among MRI sub-study participants using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the participant sustains an event and the Parent-Child/Fetus Adverse Event Report Form if the child/fetus sustains an event. Any abnormal outcome (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) must be reported in an expedited manner, as specified in Section 8.3.1, while normal outcomes must be reported within 45 days after delivery.

8.4 Treatment of Overdose

Not Applicable.

8.5 Pharmacokinetics

Not Applicable.

8.6 Pharmacodynamics

Not Applicable.

8.7 Pharmacogenetics

Optional blood samples for pharmacogenetics testing will be collected at Study Visit 1 or during following clinic visits as per SoA (Section 1.3).

- Where local regulations and IRB/IEC allow, an 8ml blood sample will be collected for DNA analysis from consenting participants. Participation in pharmacogenetic research is optional. Participants who do **not** wish to participate in the pharmacogenetic research may still participate in the study.
- In the event of DNA extraction failure, a replacement for pharmacogenetic testing may be requested from the participant. Additional informed consent will not be required to obtain a replacement sample.
- Appendix 4 provides further information on pharmacogenetic research.

8.8 Biomarkers

Not Applicable.

8.9 Immunogenicity Assessments

No Applicable.

8.10 Health Economics

Not Applicable.

9 Statistical Considerations

One interim and 1 final analysis are planned for this study.

Study data will be integrated with study data from the parent studies as required to perform the statistical analyses.

Generally, data will be analyzed descriptively with the following measures: mean with standard deviation, median with interquartile range, minimum and maximum for continuous variables and counts with percentages for categorical variables. Missing data will also be summarized. Patients' demographic factors and clinical characteristics at enrolment will be summarized descriptively as detailed above.

As the study visits are around 10 years after the initial treatment with IMP in the parent studies, it is likely that only a specific type of participants from these trials is available for follow-up. A potential selection bias will be evaluated by comparing the characteristics of those patients randomized to the parent studies and those patients included in this study.

Methodological approaches which evaluate and address this potential selection bias will be further detailed in the Statistical Analysis Plan (SAP). Differences in study populations will be considered when making inferences based upon study results. With this in mind, analyses

will generally be exploratory and for hypothesis generating purposes. Parameter estimates with associated 95% confidence intervals (CIs) will be reported for the study endpoints, as appropriate

The analytical approach for all endpoints is described below and will be further detailed in the integrated Analysis Plan (iAP).

All procedures outlined within this section will be undertaken using a SAS statistical analysis software (version 9.4 or higher).

9.1 Statistical Hypotheses

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

9.2 Sample Size Determination

No formal sample size calculation has been made for this exploratory study as enrolment is limited to eligible study participants from the parent studies (N=1,958). Therefore, as many study participants as feasibly possible will be enrolled from this group.

Using East Version 6, based on proportions of study participants that could be expected to be in a wheelchair (5%, 10% and 15%), and a range of sample size (30%, 40%, 50% and 60% participants recruited from the 1,958 participants in the parent studies), the following precision (half-width) could be achieved for the 95% CI:

% recruited	Sample Size	Proportion (π)	95% CI	Half-width
30	587	5%	[3.52 ; 6.48]	1.48%
30	587	10%	[7.97 ; 12.03]	2.03%
30	587	15%	[12.58 ; 17.42]	2.42%
40	783	5%	[3.82 ; 6.18]	1.18%
40	783	10%	[8.37 ; 11.63]	1.63%
40	783	15%	[13.06 ; 16.94]	1.94%
50	979	5%	[4.03 ; 5.97]	0.97%
50	979	10%	[8.67 ; 11.33]	1.33%
50	979	15%	[13.42 ; 16.58]	1.58%
60	1175	5%	[4.21 ; 5.79]	0.79%
60	1175	10%	[8.92 ; 11.08]	1.08%
60	1175	15%	[13.71 ; 16.29]	1.29%

9.3 Populations for Analyses

The analysis populations are specified below. Four patient cohorts will be used for the purpose of exploring all objectives of the study protocol. These will include:

- **Cohort A**: Patients who meet both the protocol inclusion and exclusion criteria and are drawn from the pooled CLARITY, CLARITY-EXT and ORACLE MS clinical trials

- **Cohort B**: Patients who meet both the protocol inclusion and exclusion criteria and are drawn from the CLARITY or CLARITY-EXT study only

- **Cohort C:** Patients who meet both the protocol inclusion and exclusion criteria and are drawn from the CLARITY-EXT study only

- **Cohort D:** Patients who meet both the protocol inclusion and exclusion criteria and are drawn from the ORACLE MS study only

The statistical analyses will generally be performed for Cohort A except for the secondary and tertiary endpoints unique to the parent studies, which will be analyzed using study participants from these parent studies only. The primary and selected secondary or tertiary analyses may be repeated by Cohort B, C and D in order to evaluate consistency of results across clinical trials.

The following subgroups will be defined:

Subgroup/Subset	Description
Subgroup Treatment Course in Cohort B	• Study participants who received placebo only (i.e. study participants that received placebo in CLARITY who did not enter CLARITY-EXT or received placebo in both CLARITY and CLARITY-EXT) • Study participants who received at least 1 dose[a] of Cladribine Tablets during either CLARITY or CLARITY -EXT but did not start the 2nd year treatment course[a] of Cladribine Tablets • Study participants who received at least 1 dose[a] of Cladribine Tablets during either CLARITY or CLARITY -EXT that started the 2nd year treatment courses[a] of Cladribine Tablets but did not start a third-year treatment course of Cladribine treatment • Study participants who received at least 1 dose[a] of Cladribine Tablets during CLARITY and CLARITY -EXT that started > 2 treatment courses[a] of Cladribine Tablets (i.e. patients who completed CLARITY and started at least the 1st year treatment course[a] in CLARITY-EXT). This corresponds to completing 2 courses of Cladribine treatment and start the third course of Cladribine treatment.

Subgroup/Subset	Description
Subset Long-term Responder	Study participants • not requiring DMD until Year 4 or later following their last dose[a] of IMP, and who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes • who started on alternate therapy (DMD) less than 4 years following their last dose[a] of IMP or who demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes.
Subset Types of Subsequent DMDs	• Platform injectable therapy (Interferon-β [Avonex®, Rebif®, Betaferon®, Extavia®, Plegridy®] or glatiramer acetate [Copaxone®]) • Monoclonal antibody disease modifying treatment • Oral disease modifying treatment • Other subsequent treatment • Off-label treatments (drugs not approved by regulatory agencies to treat MS) • No subsequent treatment
Subgroup Prior Use of DMD	• Prior use of DMD at any time in the patient's history before enrolment into CLARITY • Complementary subgroup
Subgroup HDA for Cohort B	• HDA study participants • Non-HDA study participants

DMD=disease-modifying drug, HDA=high disease activity, MS=multiple sclerosis.
[a] One dose is equivalent to one tablet. One course of IMP is defined as 1 year of treatment with IMP (2 treatment cycles [weeks]. A treatment cycle is defined as daily administration of IMP given consecutively over 4-5 days during a 28-day period. One treatment week is equivalent to 1 treatment cycle.

The primary and selected secondary or tertiary analyses may be repeated by these subgroups/subsets in order to evaluate the pattern of response.

It should be noted that the subgroup analyses on the subgroups' treatment courses and subsequent DMD do not support the comparison of any treatment effect as the definition of subgroups already is not independent from randomized treatment.

9.4 Statistical Analyses

The primary endpoint of this study will be evaluated by determining the percentage and 95% CI of patients using a wheelchair the majority of the time in the 3 months prior to Study Visit 1 or patients bedridden any time prior to Visit 1 (as defined in Section 8.1.1.1) for each Cohort and the appropriate subgroups/subsets as defined above in Section 9.3. Forest plots will also be used to display these results.

In addition, proportions adjusted for participation in previous parent studies, as well as other patient characteristics which are deemed to be prognostic for the primary endpoint will be determined applying a logistic regression model. Variables with multiple levels of discrete values will be modeled as categorical variables, and variables with continuous scales (e.g. age) may be modeled as a continuous covariate or categorized where appropriate.

The secondary endpoint, the proportion of patients with EDSS of 6.0 or higher as determined by EDSS documentation or alternative clinical description in medical records after last IMP from parent study. will be presented together with the corresponding 95% CI for each Cohort and appropriate subgroups/subsets as defined above. The results of the confidence scale of EDSS values will be presented descriptively and may be used to interpret EDSS results.

The clinical and MRI characteristics of study participants will be evaluated descriptively by the subgroup long-term responders for Cohort A.

Tertiary endpoints collected retrospectively or at Study Visit 1 will be analyzed descriptively.

Analyses of the change in EQ-5D-3L and change in cognition from the last clinical visit in the parent studies to Study Visit 1 in study participants previously treated with IMP as part of the parent studies will also be performed according to instrument developer instructions and analyzed descriptively to assess the durability of treatment effect.

Similarly, changes in MRI assessment from the last clinical visit in the parent studies to Study Visit 2 will be analyzed descriptively.

In addition, responder rates in high-disease activity (HDA) patients versus the responder rate in non-HDA patients from the CLARITY/CLARITY-EXT population will be analyzed descriptively.

Time-to-event data will be calculated from first dose of IMP in the parent study and will be presented using Kaplan-Meier estimates or cumulative incidence curves as appropriate. The analytical approach will be further detailed in the SAP.

Genetic variations will be analyzed descriptively. In addition, association of genetic variations with patients experiencing long-term response will be analyzed.

Adverse events will be summarized by number and frequency of patients with events.

Endpoint	Statistical Analysis Methods
Primary	Percentage and 95% CI
Secondary	Percentage and 95% CI
Tertiary/Exploratory	Descriptive statistics and time-to-event analyses as described above

9.4.1 Handling of Missing Data

It is anticipated that missing data will feature within the available dataset for the many of the endpoints, particularly those that are collected through retrospective medical chart review. Subsequently, should missing values constitute a substantial proportion of the endpoint data

then multiple imputation may be used in addition to the complete case approach. The multiple imputation may be repeated applying different assumptions (missing at random, missing not at random).

9.4.2 Sequence of Analyses

An interim analysis is planned to publish results when data from a minimum of 100 of patients is available from Cohort A. This data includes the primary and key secondary endpoints as well as the EQ-5D-3L; pharmacogenetics and MRI will not be included in the interim analysis. Specifics will be detailed in the iAP. Due to the exploratory nature of the study, an adjustment for multiple comparisons is not required.

The final analysis will be performed after final database lock.

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11 Appendices

Appendix 1 Abbreviations

ADR	Adverse Drug Reaction
AEs	Adverse Events
AESI	Adverse Event of Special Interest
ARR	Annualized Relapse Rate
BVMT-R	Brief Visuospatial Memory Test – Revised
CDMS	Clinically Definite Multiple Sclerosis
CI	Confidence Intervals
CNS	Central Nervous System
CRF	Case Report Form
CSF	Cerebrospinal Fluid
CUA	Combined Unique Active
DIS	Dissemination in space
DIT	Dissemination in time
DMD	Disease Modifying Drug
EC	Ethics Committees
ECG	Electrocardiography
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
EMA	European Medical Agency
EQ-5D-3L	EuroQoL-5 Dimension Questionnaire (3 level version)

FCDE	First Clinical Demyelinating Event
FS	Functional System
GCP	Good Clinical Practice
HDA	High-Disease Activity
iAP	Integrated Analysis Plan
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
PPMS	Primary Progressive Multiple Sclerosis
PRO	Patient-Reported Outcomes
PY	Person-years
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SDMT	Symbol Digit Modalities Test
SmPC	Summary of Product Characteristics
SoA	Schedule of Activities
SOC	Standard of Care
SPMS	Secondary Progressive Multiple Sclerosis

SUSAR	Suspected Unexpected Serious Adverse Reactions

Appendix 2 Study Governance

Financial Disclosure

Investigators and Sub-Investigators will provide the Sponsor with sufficient, 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

- A study main informed consent will be provided to patients or their proxy/caregiver/legal representative and this will cover both Screening and study participation. The informed consent requires a wet ink signature.
    - For deceased or lost to follow-up patients, the informed consent may be obtained from proxy/caregiver/legal representative, or an informed consent form (ICF) waiver will apply, dependent on approval by Ethics Committees, Institutional Review Boards, and/or local regulations.
- A separate informed consent will be provided for optional pharmacogenetic testing, including collection and storage of an optional blood sample. This informed consent will need to be completed at the site.
- Patients participating in the MRI sub-study will be provided with a separate informed consent for the sub-study. This informed consent will need to be completed at the site.
- The Investigator or his/her representative will explain the nature of the study to the participant or his/her proxy/caregiver/legal representative and answer all questions on the study.
- Participants must be informed that their participation is voluntary.
- Participants or their legally-authorized representative (defined as proxy or caregiver) will be required to sign a statement of informed consent that meets the requirements of local regulations; International Council for Harmonisation (ICH) guidelines; Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable; and the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or study center.
- The medical record must 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. For written informed consent, the authorized person obtaining the informed consent must also sign the ICF.
- If the ICF is updated during their participation in the study, participants must be re-consented to the most current, approved version, if still on the study.
- A copy of the ICF(s) (or an original, signed ICF in applicable countries) must be provided to the participant or the participant's proxy/caregiver/legal representative.

The original signed and dated consent will remain at the Investigator's site and must be safely archived so that it can be retrieved at any time for monitoring, auditing and inspection purposes.

- Participants who are rescreened are required to sign a new ICF.

Data Protection

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

Study Administrative

- The study aims to involve approximately 108 sites in 30 countries across North America, Europe and Asia Pacific.

  Sites that participated in CLARITY, CLARITY-EXT or ORACLE MS will be invited to participate in this study.
- The Steering Committee members listed on the title page represent all Investigators for decisions and discussions on this study, per ICH Good Clinical Practices (GCPs). The Steering Committee members 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.
- The study will appear in the following clinical studies registries: clinicaltrials.gov.
- The contract research organization tasked with study management, regulatory and start up, monitoring, epidemiology and medical writing, data management, safety management, clinical event validation and adjudication services and central laboratory for storage of pharmacogenetic samples is IQVIA (500 Brook Drive, Green Park, Reading, Berkshire, RG2 6UU, United Kingdom).
- The third-party service provider tasked for MRI sub-study set up and quality control of imaging collected for the sub-study is BIOCLINICA (211 Carnegie Center Drive, Princeton, New Jersey 08540, USA).
- The third-party service provider tasked for MRI central reading of imaging collected for the sub-study is SIENA IMAGING (Via Fiorentina 1 – 53100 – Siena (SI), Italy).
- The third-party service provider tasked for BVMT-R central reading of the respective cognitive testing collected for the study is PPD

- The third-party service provider tasked for Biostatistical services on the study is Cytel Inc. (675 Massachusetts Avenue, Cambridge, MA 02139, USA).
- Responsibilities regarding safety and medical monitoring are described in the Safety Monitoring Plan and the Medical Monitoring Plan, respectively. Details of structures and associated procedures will be defined in a separate Study Reference Manual.

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 International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The Investigator must submit the protocol, protocol amendments (if applicable), ICF, summary of product characteristics (SmPC), and other relevant documents (e.g., advertisements) to an IRB/IEC and the IRB/IEC must 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 shall meet good local standards, as applicable.

Clinical Study Report

After study completion, the Sponsor or delegate will write a clinical study report in consultation with the Steering Committee or other relevant study-appointed committees or groups.

Publication

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows Merck to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. Per standard editorial and ethical practice, the Sponsor will generally support 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

- After completion of the study, a Clinical Study Report (including results on all study objectives except, in case not available in time, results of the pharmacogenetic testing) according to ICH Topic E3 will be written by the Sponsor or the designated CRO.
- Analyses of pharmacogenetics testing will be completed approximately 2 years after study completion and will be presented in a clinical study report addendum, if not reported in the Clinical Study Report.
- The Investigators will inform the Sponsor in advance of any plans to publish or present data from the study. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations etc.), either in whole or in part, by Investigators or their representatives will require pre-submission review by the Sponsor.
- The Sponsor will not suppress or veto publications but maintains the right to delay publication in order to protect intellectual property rights.
- The study will be posted on clinicaltrials.gov.

Data Quality Assurance

- All participant study data will be recorded on electronic case report form (eCRFs) 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 case report form (CRF). Details for managing CRFs are in the Study Reference Manual.
- For PRO data (e.g., QoL and cognitive assessments), paper PRO will be used.
- The Investigator must maintain accurate documentation (source data) that supports the information in the CRF.
- The Investigator must 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.
- 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.
- 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.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator 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 must keep a paper or electronic file (medical file and original medical records) at the site for each study participant. The file must identify each participant, contain the following demographic and medical information for the participant, and should 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 or study intervention, if applicable
- All source data must be filed (e.g., CT or MRI scan images, ECG recordings, and laboratory results). Each document must have the participant number and the procedure date; ideally, printed by the instrument used for the procedure. As necessary, medical

evaluation of these records should be performed, documented, signed and dated by the Investigator.

- Data recorded on printed or electronic CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- The study monitors will use printouts of electronic files for source data verification. These printouts must 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 Monitoring Plan.

Study and Site Start and Closure

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

Appendix 3 Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

Definitions

Adverse Event

An AE is any untoward medical occurrence in a participant administered a pharmaceutical product, regardless of causal relationship with this treatment. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, regardless if it is considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE.

Investigators must assess the severity of AEs per the Qualitative Toxicity Scale, as follows:

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

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

Severe: Significant impairment of functioning: the participant is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to study intervention (including any other non-study interventions, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the investigational medicinal product (IMP) treatment received in the parent study include, but may not be limited to, temporal relationship between the AE and the IMP treatment received in the parent study, known side effects of the IMP treatment received in the parent study, medical history, concomitant medication, course of the underlying disease, and the MRI procedure (if applicable).

Unrelated: Not reasonably related to the study intervention. AE could not medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the study intervention. AE could medically (pharmacologically/clinically) be attributed to the study intervention under study in this clinical study protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (e.g., on an ECG trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to study intervention discontinuation or are considered otherwise medically important by the Investigator. A positive test for COVID-19, with or without the presence of symptoms, would be considered an AE. If a laboratory abnormality fulfills

these criteria, the identified medical condition (e.g., anemia or increased alanine amino transferase) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening. Life-threatening refers to an event in which the participant is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe
- Requires inpatient hospitalization or prolongs an existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is otherwise considered to be medically important. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the participant or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

For the purposes of reporting, any suspected transmission of an infectious agent via a study intervention is also considered an SAE, as specified below for reporting SAEs and adverse events of special interest (AESIs).

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations are not considered SAEs. 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.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial study visit that do not worsen in severity or frequency during the study are defined as Baseline Medical Conditions and are not to be considered AEs.

MS Relapses

In this protocol, symptoms and signs of relapse or worsening of MS 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 the IMP (i.e. worsening is not consistent with the anticipated natural progression of the disease).

Adverse Events of Special Interest

AEs of interest for this study defined in the Section 6.9 should be considered as medically significant AEs.

Recording and Follow-Up of AE and/or SAE

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

Specific guidance is in the CRF Completion and Monitoring Conventions provided by the Sponsor.

Reporting Serious Adverse Events and Adverse Events of Special Interest

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee using the electronic SAE report form in the electronic data capture (EDC) system. Any ADRs (assessed as related to cladribine by the Investigator after the End of Trial Visit in the parent study CLARITY/ORACLE/CLARITY-EXT) must be recorded in the eCRF as well. If the ADR information is captured in the subject's medical chart already at the time of enrolment then the event is not considered to be of new awareness and it is expected to be reported in the Medical History page (e.g. awareness date prior to ICF date). If the ADR is reported by the patient at the time of enrolment or after that then the event is considered of new awareness, and it is expected to be reported in the ADR page (e.g. awareness date is after ICF date).Reporting of SAEs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

In exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases, an electronic SAE report form must be completed immediately thereafter.

Relevant pages from the CRF may be provided in parallel (e.g., medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (e.g., laboratory results, hospital report, autopsy report).

The Investigator must respond to any request for follow-up information (e.g., additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor

or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the study monitor, although in exceptional circumstances the drug safety department may contact the Investigator directly to obtain further information or to discuss the event.

Adverse Events of Special Interest

In the event of a non-serious AESI, the Investigator will notify the Sponsor/designee by completing the electronic AESI Report Form in the EDC system. Serious AESIs must be reported in an expedited manner as SAEs, as outlined above. Reporting of non-serious AESIs using a paper report form is required as a back-up method only for an EDC system failure. Names, addresses, and telephone and fax numbers will be included on the paper report form. All information from the paper form must be transcribed into the electronic form as soon as the system becomes available.

Appendix 4 Pharmacogenetics

Use/Analysis of DNA

- Genetic variation may impact a participant's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact study intervention absorption, distribution, metabolism, and excretion; mechanism of action of the study intervention; disease etiology; and/or molecular subtype of the disease being treated.
- DNA samples will be analyzed for association of genetic variations with clinical outcome measures. Additional analyses may be conducted if it is hypothesized that this may help further understand the clinical data.
- In addition, DNA samples will be used for research related to mechanism of action, and related diseases. They may also be used to develop tests or assays, including diagnostic tests related to mechanism of action and indication. Pharmacogenetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome or analysis of the entire genome (as appropriate).
- The results of pharmacogenetic analyses will be reported in the Clinical Study Report or a separate study summary within approximately 2 years after the end of the study.
- Details on processes for collection and shipment of these samples can be found in the Q2 Solutions Laboratory manual and flow chart. Post-study, the Sponsor will store the DNA samples in a secure storage space with adequate measures to protect confidentiality.
- Retention time and possible analysis of DNA sample after the study ends are specified in the respective ICF.

Appendix 5 Expanded Disability Status Scale (EDSS)

General

- The Evaluating Physician will complete the Expanded Disability Status Scale (EDSS).
- The same individual should remain as the Evaluating Physician for each patient, except when exceptional circumstances make this impossible.
- Prior to each neurological assessment, the Evaluating Physician **should not** refer to any previous neurological assessments carried out on that patient.
- The current EDSS will be recorded (i.e. the EDSS as assessed during the visit).

EDSS SCORING

- **0.0** Normal neurological exam [all grade 0 in all Functional System (FS) scores*]
- **1.0** No disability, minimal signs in one FS* (i.e., grade 1)
- **1.5** No disability, minimal signs in more than one FS* (more than 1 FS grade 1)
- **2.0** Minimal disability in one FS (one FS grade 2, others 0 or 1)
- **2.5** Minimal disability in 2 FS (2 FS grade 2, others 0 or 1)
- **3.0** Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in 3 or 4 FS (3 or 4 FS grade 2, others 0 or 1) though fully ambulatory
- **3.5** Fully ambulatory but with moderate disability in one FS (one grade 3) and one or 2 FS grade 2; or 2 FS grade 3 (others 0 or 1) or 5 grade 2 (others 0 or 1)
- **4.0** Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters
- **4.5** Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters
- **5.0** Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)
- **5.5** Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0)
- **6.0** Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than 2 FS grade 3+)

- **6.5** Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than 2 FS grade 3+)
- **7.0** Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone)
- **7.5** Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+)
- **8.0** Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems)
- **8.5** Essentially restricted to bed much of day; has some effective use of arms(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems)
- **9.0** Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+)
- **9.5** Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, mostly grade 4+)
- **10.0** Death due to MS

*Excludes cerebral function grade 1

Note 1: EDSS steps 1.0 to 4.5 refer to patients who are fully ambulatory and the precise step number is defined by the FS score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in FS scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

Scores of 4.5 and above are determined by ambulation distances as follows:
4.0 Able to walk at least 500 meters without aid
4.5 Able to walk 300-499 meters without aid
5.0 Able to walk 200-299 meters without aid
5.5 Able to walk 100-199 meters without aid
6.0 Able to walk 5-99 meters without aid or with unilateral assistance is able to walk at least 100 meters
6.5 Bilateral assistance required to walk but able to walk at least 20 meters; or unilateral assistance needed but able to walk between 5-99 meters
7.0 Only able to walk between 1- 5 meters even with assistance
7.5 Unable to walk more than a few steps (i.e., not able to walk at all or able to walk a maximum of about 1 meter)
8.0-9.5 Investigator judgment

The guiding principle: if a patient fails to meet the criteria of a given level, they are automatically assigned to the next higher level. If a patient does not need aids to walk (i.e., walks unassisted) but can only walk 50 meters, they are to be considered EDSS 6.0 since they do not satisfy the criteria for EDSS 5.5.

Appendix 6 2017 Mc Donald Criteria (From Thompson, 2018)

Table: The 2017 McDonald criteria for diagnosis of multiple sclerosis in patients with an attack at onset

	Number of lesions with objective clinical evidence	**Additional data needed for a diagnosis of multiple sclerosis**
≥2 clinical attacks	≥2	None*
≥2 clinical attacks	1 (as well as clear-cut historical evidence of a previous attack involving a lesion in a distinct anatomical location†)	None*
≥2 clinical attacks	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡
1 clinical attack	≥2	Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶
1 clinical attack	1	Dissemination in space demonstrated by an additional clinical attack implicating a different CNS site or by MRI‡ AND Dissemination in time demonstrated by an additional clinical attack or by MRI§ OR demonstration of CSF-specific oligoclonal bands¶

If the 2017 McDonald Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is multiple sclerosis. If multiple sclerosis is suspected by virtue of a clinically isolated syndrome but the 2017 McDonald Criteria are not completely met, the diagnosis is possible multiple sclerosis. If another diagnosis arises during the evaluation that better explains the clinical presentation, the diagnosis is not multiple sclerosis. An attack is defined in panel 1. *No additional tests are required to demonstrate dissemination in space and time. However, unless MRI is not possible, brain MRI should be obtained in all patients in whom the diagnosis of multiple sclerosis is being considered. In addition, spinal cord MRI or cerebrospinal fluid (CSF) examination should be considered in patients with insufficient clinical and MRI evidence supporting multiple sclerosis, with a presentation other than a typical clinically isolated syndrome, or with atypical features. If imaging or other tests (e.g., CSF) are undertaken and are negative, caution needs to be taken before making a diagnosis of multiple sclerosis, and alternative diagnoses should be considered. †Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for one past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic for a previous inflammatory demyelinating attack;

at least one attack, however, must be supported by objective findings. In the absence of residual objective evidence, caution is needed. ‡The MRI criteria for dissemination in space are described in panel 5. §The MRI criteria for dissemination in time are described in panel 5.

¶The presence of CSF-specific oligoclonal bands does not demonstrate dissemination in time per se but can substitute for the requirement for demonstration of this measure.

Panel 3: Considerations to help avoid misdiagnosis of multiple sclerosis

- Recognize that the McDonald criteria were not developed to differentiate multiple sclerosis from other conditions but to identify multiple sclerosis or a high likelihood of the disease in patients with a typical clinically isolated syndrome once other diagnoses have been deemed unlikely.

- Integration of the history, examination, imaging, and laboratory evidence by a clinician with multiple sclerosis-related expertise remains fundamental in making a reliable diagnosis of multiple sclerosis or an alternative diagnosis. In addition to confirming dissemination in space and time, diagnostic rigor in the interpretation of clinical data, imaging findings, and test results is necessary.

- In the absence of a clear-cut typical clinically isolated syndrome (panel 1), caution should be exercised in making the diagnosis of multiple sclerosis, and the diagnosis should be confirmed by further clinical and radiological follow-up. In such cases, the clinician should consider postponing making a definitive diagnosis and initiation of long-term disease-modifying therapies, pending longer follow-up to accumulate additional evidence supporting the diagnosis.

- Caution should be taken in accepting a historical event as an attack in the absence of contemporaneous or current objective evidence providing corroboration.

- The threshold for additional testing should be low, including for spinal cord MRI or CSF examination in the following situations: when clinical and brain MRI evidence supporting a diagnosis of multiple sclerosis is insufficient, particularly if initiation of long-term disease-modifying therapies are being considered; when there is a presentation other than a typical clinically isolated syndrome, including patients with a progressive course at onset (primary progressive multiple sclerosis); when there are clinical, imaging, or laboratory features atypical of multiple sclerosis; and in populations in which multiple sclerosis is less common (e.g., children, older individuals, or non-white populations).

Panel 4: 2017 revisions to the McDonald diagnostic criteria for multiple sclerosis

- In a patient with a typical clinically isolated syndrome and fulfillment of clinical or MRI criteria for dissemination in space and no better explanation for the clinical presentation, demonstration of CSF-specific oligoclonal bands in the absence of other CSF findings atypical of multiple sclerosis allows a diagnosis of this disease to be made. This recommendation is an addition to the 2010 McDonald criteria.

- Symptomatic and asymptomatic MRI lesions can be considered in the determination of dissemination in space or time. MRI lesions in the optic nerve in a patient presenting with optic neuritis remain an exception and, owing to insufficient evidence, cannot be used in fulfilling the McDonald criteria. In the 2010 McDonald criteria, the symptomatic lesion in a patient presenting with brainstem or spinal cord syndrome could not be included as MRI evidence of dissemination in space or time.

- Cortical and juxtacortical lesions can be used in fulfilling MRI criteria for dissemination in space. Cortical lesions could not be used in fulfilling MRI criteria for dissemination in space in the 2010 McDonald criteria.

- The diagnostic criteria for primary progressive multiple sclerosis in the 2017 McDonald criteria remain the same as those outlined in the 2010 McDonald criteria, aside from removal of the distinction between symptomatic and asymptomatic MRI lesions and that cortical lesions can be used.

- At the time of diagnosis, a provisional disease course should be specified (relapsing-remitting, primary progressive, or secondary progressive) and whether the course is active or not, and progressive or not based on the previous year's history. The phenotype should be periodically re-evaluated based on accumulated information. This recommendation is an addition to the 2010 McDonald criteria.

Panel 5: 2017 McDonald criteria for demonstration of dissemination in space and time by MRI in a patient with a clinically isolated syndrome

- Dissemination in space can be demonstrated by one or more T2-hyperintense lesions* that are characteristic of multiple sclerosis in 2 or more of 4 areas of the central nervous system (CNS): periventricular,† cortical or juxtacortical, and infratentorial brain regions, and the spinal cord

- Dissemination in time can be demonstrated by the simultaneous presence of gadolinium-enhancing and non-enhancing lesions* at any time or by a new T2-hyperintense or gadolinium-enhancing lesion on follow-up MRI, with reference to a baseline scan, irrespective of the timing of the baseline MRI

*Unlike the 2010 McDonald criteria, no distinction between symptomatic and asymptomatic MRI lesions is required. †For some patients—e.g., individuals older than 50 years or those with vascular risk factors—it might be prudent for the clinician to seek a higher number of periventricular lesions.

Appendix 7 Sponsor Signature Page

Study Title:	Evaluating the Long-Term Outcomes and Durability of Effect Following Treatment with Cladribine Tablets for Multiple Sclerosis: An Exploratory Phase IV Ambispective Study of Patients Who Previously Participated in the CLARITY/CLARITY-EXT and ORACLE MS Clinical Trials
Regulatory Agency Identifying Numbers:	EudraCT number: 2019-000069-19
Clinical Study Protocol Version:	03 July 2020 / Version 2.0

I approve the design of the clinical study:

PPD

03 July 2020
Date of Signature

Name, academic degree:	PPD
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Appendix 8 Principal Investigator Signature Page

Study Title:	Evaluating the Long-Term Outcomes and Durability of Effect Following Treatment with Cladribine Tablets for Multiple Sclerosis: An Exploratory Phase IV Ambispective Study of Patients Who Previously Participated in the CLARITY/CLARITY-EXT and ORACLE Trials
Regulatory Agency Identifying Numbers:	EudraCT number: 2019-000069-19
Clinical Study Protocol Version:	03 July 2020/Version 2
Site Number:	

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

_____ _____

Signature Date of Signature

Name, academic degree:	[Insert Name and highest degree or for a single center study, insert from Title Page]
Function/Title:	
Institution:	[Insert Name of Institution or for a single center study, insert from Title Page]
Address:	[Insert Full Mailing Address (e.g., Street, City, postal code, and Country)]
Telephone number:	[Insert Full number, including country code]
Fax number:	[Insert Full number, including country code or "Not Applicable"]
E-mail address:	