Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS700568_0070
Title	Oral CLADribine in patients that Change from first-line Disease Modifying Treatments for Multiple Sclerosis: a pROspective effectivenesS and Safety study (CLAD CROSS)
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Approval Page

Integrated Analysis Plan: MS700568_0070

Oral CLADribine in patients that Change from first-line Disease Modifying Treatments for Multiple Sclerosis: a pROspective effectivenesS and Safety study

(CLAD CROSS)

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1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE	Adverse Event
ANOVA	Analysis of VARIANCE
ARR	Annualized Relapse Rate
ATC	Anatomical Therapeutic Chemical classification
BOCF	Baseline Observation Carried Forward
CI	Confidence Interval
(e)CRF	(electronic) Case Report Form
CM	Concomitant Medication
CSR	Clinical Study Report
CUA	Cumulative Unique Active
DMD	Disease Modifying Drug
DMF	Dimethyl fumarate
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
FAS	Full Analysis Set
HRQoL	Health-Related Quality of Life
IAP	Integrated Analysis Plan
ICF	Informed Consent Form
IFN	Interferon
IPD	Important Protocol Deviations
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSIS-29	Multiple Sclerosis Impact Scale
NR	Non-responder
PT	Preferred Term
QoL	Quality of Life
RRMS	Relapsing-remitting Multiple Sclerosis
SAE	Serious Adverse Event

SAS	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TEAESI	Treatment-Emergent Adverse Event of Special Interest
TSQM	Treatment Satisfaction Questionnaire for Medication
T25FW	Timed 25-Foot Walk
VAS	Visual Analogue Scale
WHO-DD	World Health Organization Drug Dictionary
9HPT	9-Hole Peg Test

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	29 JUN 2020	PPD	First version
1.1	25 OCT 2021		Protocol amendment integrated including 2 interim analyses Removal of Screening Log reference and external source data as not feasible to collect. Added list of outputs included in each interim analysis
1.2	11 NOV 2021		Section 9.5 updated adding table describing windowing
2.0	17 NOV 2021		Section 9.5 updated removing windowing for primary and secondary endpoint

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the final analyses of data collected for protocol MS700568_0070. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is prepared in compliance with International Conference on Harmonization (ICH) E9 and describes analyses planned in the study Protocol Section 9.7 (Data Analysis) and any protocol amendment.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP Section
Primary		
To study the change in annualized relapse rate (ARR) in patients switching from first-line Disease Modifying Drugs (DMDs) to Cladribine tablets, between the 12-month pre-baseline period and over the 12 months period before End of Study follow-up (2 years)	**Effectiveness:** Difference in ARR between the pre-baseline 12-month period and over the 12 months period before the End of Study follow-up (2 years)	14.1
Secondary		
To assess change in ARR in patients switching from first-line DMDs to Cladribine tablets, between the 12-month pre-baseline period and over the 12 months period after initiation of Cladribine tablets (1 year)	**Effectiveness:** Difference in ARR between the pre-baseline 12-month period and over the 12 months period after the start of cladribine (1 year)	14.2

Objectives	Endpoints (Outcome Measures)	IAP Section
To assess disability progression. Disability progression is defined as progression on ⩾1 of 3 components (Expanded Disability Status Scale [EDSS], Timed 25-Foot Walk [T25FW], and/or 9-Hole Peg Test [9HPT]) confirmed ⩾ 24 weeks apart and with a ⩾20% minimum threshold change for T25FW and 9HPT. T25FW and 9HPT are optional and will be performed if done as per routine practice. Progression on EDSS is defined as at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score is 0.	**Effectiveness:** Percentage of patients with 6-month disability progression at the end of the study follow-up period (2 years), measured as EDSS, T25FW (optional) and 9-HPT (optional).	14.3
To assess disability improvement. Disability Improvement is defined as an improvement on ⩾1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ⩾24 weeks apart and with a ⩾20% minimum threshold change for T25FW and 9HPT. T25FW and 9HPT are optional and will be performed if done as per routine practice. Improvement on EDSS is defined as a decrease in EDSS by at least 1 point (1.5 points if baseline EDSS was 1.5).	**Effectiveness:** Percentage of patients with 6-month disability improvement at the end of the study follow-up period (2 years), measured as EDSS, T25FW (optional) and 9-HPT (optional)	14.4
To assess safety of Cladribine tablets in the real world, at two years	**Safety:** Occurrence of adverse events and of serious adverse events	15
To assess Quality of Life and treatment satisfaction	**Quality of Life:** • Multiple Sclerosis Impact Scale (MSIS-29) • Treatment Satisfaction Questionnaire for Medication (TSQM) v1.4 • CCI [redacted]	16.1 16.2 16.3
To assess treatment adherence	**Drug Use:** Percentage of cladribine tablets taken versus prescribed dose	13
CCI [redacted]	CCI [redacted]	16.1 16.2 16.3
Tertiary/Exploratory		
For those patients that the treating physicians decide to prescribe a Magnetic Resonance Imaging (MRI) at baseline and/or Year 2: 1. To compare MRI characteristics between baseline and Years 1 and 2 2. To compare MRI characteristics between the 12-month pre-baseline and post-baseline results (Years 1 and 2)	**Effectiveness:** Number of MRI lesions (T2, T1 Gd+, Cumulative Unique Active [CUA]) at baseline and years 1 and 2	16.4

Objectives	Endpoints (Outcome Measures)	IAP Section
To study effectiveness in 5 subgroups, defined according to the pre-baseline DMD treatment (Interferon [IFN]- ß 1a / IFN- ß 1b / Glatiramer Acetate, Teriflunomide, Dimethyl fumarate [DMF]).	All effectiveness outcomes for primary and secondary objectives will be analyzed for the 5 defined subgroups	14.1.3 14.2.3 14.3.3 14.4.3

6 Overview of Planned Analyses

Two descriptive interim analyses will be performed, respectively when 30% and 60% of the patients have completed the 12-month follow-up visit, to check if pre-baseline ARR estimate and its variance are consistent with the sample size assumptions. An alpha adjustment for the multiplicity of the analysis will be introduced if the interim analysis will lead to change in sample size strategy. The full list of outputs included in each interim analysis is available in Appendix 18.2.

This study will have a final analysis after database lock. The final analysis will be performed for all patients at the end of study. All final, planned analyses identified in the study protocol and this IAP will be performed only after the last participant has completed the study with all study data in-house, all data queries resolved, and the database is locked. Statistical analyses will be performed on the basis of raw Statistical Analysis Software (SAS) datasets extracted from the electronic Case Report Form (eCRF). These raw data contain as clean as possible eCRF data. The database lock is expected to occur approximately 1 month after Last Patient Last Visit.

A data review meeting will be held prior to the database lock, using a pre-database lock transfer that will also be used for dry-run purpose. In addition, no database can be locked until this IAP has been approved.

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the analyses planned per protocol.

8 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

Full Analysis Set

The Full Analysis Set (FAS) is defined as all the patients who provided informed consent and who received at least one dose of Cladribine.

8.2 Subgroup Definition and Parameterization

Subgroup analyses will be performed on primary and some secondary effectiveness endpoints as defined below. All subgroup analyses will be exploratory, no adjustment for multiplicity will be performed.

For the definition of subgroup level data, data will be taken, as documented in the eCRF. The category "missing" will not be included in any subgroup analysis.

The following subgroups will be defined:

- Pre-baseline most recent Disease Modifying Drug (DMD):
  - Interferon (IFN)- ß 1a *[IFNβ 1a (Rebif®) 22 µg t.i.w s.c.; IFNβ 1a (Rebif®) 44 µg t.i.w s.c.; IFNβ 1a (Avonex®) 30µg q.w. i.m.; IFNβ 1a (Plegridy®) 94µg q2wk s.c.; IFNβ 1a (Plegridy®) 125µg q2wk s.c.]*
  - IFN- ß 1b *[IFNβ 1b (Betaferon®, Extavia®) 250µg every other day]*
  - Glatiramer Acetate *[Glatiramer acetate (Copaxone, CLIFT) 20mg q.d. s.c.; Glatiramer acetate (Copaxone, CLIFT) 40mg t.i.w s.c.]*
  - Teriflunomide *[Teriflunomide 14mg]*
  - Dimethyl fumarate (DMF) *[Dimethyl fumarate 120mg; Dimethyl fumarate 240mg]*

9 General Specifications for Data Analyses

This section describes any general specifications not included in subsequent sections. This study is a single cohort study and no comparison between groups is planned. The "start date" for this study is the start date of treatment with Cladribine.

Continuous variables will be summarized using descriptive statistics, i.e. the number of patients with non-missing values (n), the number of patients with missing values (nmiss), mean, standard deviation (SD), median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. If there are no missing values, the number of patients with missing values (nmiss) should be indicated by a 0. Mean, median, Q1, Q3, minimum and maximum will be reported with the same number of decimal places as collected in raw data while SD will be reported with one extra decimal place.

Qualitative variables will be summarized by frequency counts and percentages. Unless otherwise stated the calculation of proportions will be based on the number of patients of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

The overall significance level is 5% two-sided. Confirmatory statistical tests will be performed on the primary outcome only. All other statistical tests mentioned in this IAP are to be regarded as exploratory. Exploratory statistical tests comparing study treatment groups will be performed two-sided. If confidence intervals (CIs) are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

In order to provide overall estimates of treatment effects, data will be pooled across sites. The "site" factor will not be considered in statistical models or for subgroup analyses due to the high number of participating sites in contrast to the anticipated small number of patients treated at each site.

All analyses will be performed using SAS® Software version 9.4 or higher. R version 3.2.2 or higher may be used to create some of the figures in case it provides a better alternative layout.

9.1 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to the first study treatment administration will be used as the baseline measurement. If an assessment is performed on the same day as the start of treatment it will be assumed that it was performed prior to it and will be considered as baseline. Since enrollment is planned up to the second treatment week of the first treatment year, baseline data collected will occur retrospectively. This is according to the study design since the decision to prescribe the treatment should be prior to study enrollment. Administration of Patient questionnaires such as HRQoL and Disability Assessments may be administered after cladribine administration if enrollment occurs after treatment administration. For those cases, baseline measurement will be the data collected at the Baseline visit.

Absolute and percent changes from baseline are defined as

absolute change = visit value – baseline value

percent change = 100 × (visit value – baseline value)/baseline value

9.2 Study Day / Study Treatment Day

Day 1 is the day of the start of study treatment, the day before is Day -1 (no Day 0 is defined). Study day/Study treatment day is defined relative to Day 1.

9.3 Definition of Duration and 'time since' Variables

Duration in days will be calculated by the difference of start and stop date + 1 (e.g. length of follow-up (Months) = End of Study date – date of Cladribine treatment + 1) if not otherwise specified. For events that are "ongoing", the duration will be calculated based on the date of the last contact instead of the date of death.

The time since an event (e.g. time since the first diagnosis) will be calculated as reference date minus date of the event.

9.4 Conversion Factors

The following conversion factors will be used to convert days into months or years:

1 week = 7 days, 1 month = 30.4375 days, 1 year = 365.25 days.

9.5 Windowing and Unscheduled Visits

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

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

In addition to the baseline data, data collection is planned at 4 supplementary visits according to routine practice: at months 6 (Visit 1), 12 (Visit 2), 18 (Visit 3) and 24 approximately (Visit 4).

Apart from Baseline visit, PROs assessments will be derived considering a 6 months (± 30 days) frequency and will be calculated using study day as shown in table below:

Visit Name	Derivation
Baseline	Baseline visit [a]
Months 6 (Visit 1)	150 days ≤ STUDY DAY ≤ 210 days
Months 12 (Visit 2)	335 days ≤ STUDY DAY ≤ 395 days
Months 18 (Visit 3)	510 days ≤ STUDY DAY ≤ 570 days
Months 24 (Visit 4)	700 days ≤ STUDY DAY ≤ 760 days

[a] Baseline visits will not be remapped as the starting of the observation and will be assigned as per eCRF visit.

Out of windows data will be included in a sensitivity analysis for HRQoL.

As per the study design, the definition of unscheduled visits does not exist. According to the instructions provided to the sites, when more than 1 appointment occurs within a time-period (e.g. 6-Months), only the appointment closer to the upper limit of that visit will be recorded in the eCRF.

9.6 End of Study, Date of last Contact and Lost to Follow-up

End of study is defined as the last visit performed by the patient within the period of 24-Months ± 3 months after baseline.

A patient will be considered lost to follow-up when he/she prematurely discontinued the study, meaning that he/she discontinued the study prior to finalizing the 24-Months observational period. As per the protocol and eCRF options, a patient can be lost to follow-up due to:

- Withdrew consent from study
- Death
- Change to other DMD
- Other reason (e.g. not able to contact the patient)

As per the study design, discontinuation of treatment does not imply lost to follow-up. Patients who discontinue the treatment will continue to be followed for safety reasons until the 24-Months observational period ends or unless they switch to another DMD treatment.

The date of the last contact will be derived as:

- End of study date, for patients completing the observational period
- Date of death for patients lost to follow-up due to death
- Maximum of the following event dates, when complete dates available, for lost to follow-up patients when lost to follow-up cause is not death:
    - Maximum available date of visit
    - Study drug start
    - Adverse Event (AE) start and end dates
    - Concomitant Medication (CM) start and end dates
    - Date of Quality of Life (QoL) questionnaires (MSIS-29, CCI and Treatment Satisfaction Questionnaire for Medication [TSQM]).

Only dates associated with patient actual examinations reported in the eCRF will be used in the derivation. Dates associated with a technical operation unrelated to patient status such as the date a blood sample was processed will not be used.

9.7 Definition of On-treatment Period

The on-treatment period is defined as the date of the first dose of study treatment to the date of the last contact. Due to the posology and long-term effects of Cladribine, a patient is on-treatment from the first dose received of Cladribine until the follow-up period ends.

9.8 Imputation of Missing Data

Unless specified otherwise in other IAP sections, all data will be evaluated as observed, and no imputation method for missing values will be used.

Treatment dates are not expected to be incomplete as they are required fields in the eCRF and no partial dates are allowed. Specific rules for classification of AEs and CMs for analysis purpose are presented below.

Missing statistics, e.g. when they cannot be calculated, should be presented as "nd". For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as "nd".

9.8.1 TEAE classification

Rules presented in Table 1 will be used for classification of AEs as Treatment-Emergent Adverse Events (TEAEs). An AE is considered a TEAE if started on or after study treatment start date.

Table 1 TEAE Classification rules

Start date of AE			TEAE classification
Day	**Month**	**Year**	
UNK	UNK	UNK	TEAE
UNK	UNK	< Treatment start (year)	Not TEAE
UNK	UNK	≥ Treatment start (year)	TEAE
UNK	< Treatment start (month and year)		Not TEAE
UNK	≥ Treatment start (month and year)		TEAE
< Treatment start (complete date)			Not TEAE
≥ Treatment start (complete date)			TEAE

AE = Adverse event; TEAE = Treatment-emergent adverse event; UNK = Unknown

9.8.2 CM classification

Rules presented in Table 2 will be used for the classification of medications and other procedures as concomitant or previous. A medication can simultaneously be concomitant and previous in cases where medication started prior to treatment but it is ongoing at baseline.

Table 2 CM Classification rules

Start date of CM			Concomitant classification	Previous classification
Day	**Month**	**Year**		
UNK	UNK	UNK	Concomitant if Ongoing Not concomitant if not Ongoing	Previous
UNK	UNK	< Treatment start (year)	Concomitant if Ongoing Not concomitant if not Ongoing	Previous
UNK	UNK	≥ Treatment start (year)	Concomitant	Not previous
UNK	< Treatment start (month and year)		Concomitant if Ongoing Not concomitant if not Ongoing	Previous
UNK	≥ Treatment start (month and year)		Concomitant	Not previous
< Treatment start (complete date)			Concomitant if Ongoing	Previous

Start date of CM			Concomitant classification	Previous classification
Day	Month	Year		
			Not concomitant if not Ongoing	
≥ Treatment start (complete date)			Concomitant	Not previous

CM = Concomitant medications; UNK = Unknown

9.9 Scoring of HRQoL Data

Unless otherwise specified, Health-Related Quality of Life (HRQoL) questionnaires will be scored using their published administration and scoring manual. For items with missing responses, the response will be managed as per the scoring manual.

9.9.1 MSIS-29

The Multiple Sclerosis Impact Scale (MSIS-29) is a 29-item self-report measure with 20 items associated with a physical scale and 9 items with a psychological scale. Items ask about the impact of multiple sclerosis (MS) on day-to-day life in the past two weeks. All items have 5 response options: 1 "not at all" to 5 "extremely". Each of the two scales are scored by summing the responses across items, then converting to a 0-100 scale where 100 indicates greater impact of disease on daily function (worse health) (RIMS - Rehabilitation in Multiple Sclerosis, s.d.).

The physical impact score is computed by summing items number 1-20 inclusive (observed score). This score can then be transformed to a score on a scale of 0-100 using the formula below:

$$\frac{[100 \times (observed\ \ score - 20)]}{(100 - 20)}$$

The psychological impact score is computed by summing items number 21-29 inclusive (observed score). This score can then be transformed to a score on a scale of 0-100 using the formula below:

$$\frac{[100 \times (observed\ \ score - 9)]}{(45 - 9)}$$

For respondents with missing data, but where at least 50% of the items in a scale have been completed, a respondent–specific mean score computed from the completed items can be computed. This is achieved by calculating an average score from the available items and assign this average score to the missing items. Then, the normal score as per the formulas above can be calculated (RIMS - Rehabilitation in Multiple Sclerosis, s.d.).

9.9.2 TSQM v1.4

Version 1.4 of the TSQM consists of 14 items that results in four specific domains: Effectiveness, Side Effects, Convenience, and one global scale item, Global Satisfaction. Scores for each domain are computed by adding the TSQM items in each domain and then transforming the composite score into a value ranging from 0 to 100. Of note, a score can be computed for a domain only if no

more than one item is missing from that domain. The calculations specific to each domain are presented in detail below (IQVIA, 2019).

Global Satisfaction

- ([(Sum (Item 12 to Item 14)) – 3] divided by 14) × 100

If Item 12 or 13 is missing

- ([(Sum (the two completed items)) – 2] divided by 10) ×100

If Item 14 is missing

- ([(Sum (Item 12 and Item 13)) – 2] divided by 8) × 100

Effectiveness

- ([(Item 1 + Item 2 + Item 3) – 3] divided by 18) × 100

If one item is missing

- ([Sum (the two completed items)) – 2] divided by 12) × 100

Side Effects

If Question 4 is answered 'No'

- Score = 100

If Question 4 is not answered 'No'

- ([Sum (Item 5 to Item 8) – 4] divided by 16) × 100

  If one item is missing

  - ([(Sum (the three completed items)) – 3] divided by 12) × 100

Convenience

- ([Sum (Item 9 to Item 11) – 3] divided by 18) × 100

If one item is missing

- ([(Sum (the two completed items) – 2] divided by 12) × 100

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10 Study Patients

The subsections in this section include specifications for reporting participant disposition and study treatment/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Patients and Discontinuations

The number and percentage of patients in each of the below disposition categories will be presented. Percentages will be presented with respect to the number of treated patients.

- Total number of patient entered, based on completion of "Study Entry" eCRF form and reason for screen failure
- Number and percentage of enrolled patients
- Number and percentage of non-treated
- Number and percentage of treated patients (i.e. patients who gave informed consent and received at least one dose of cladribine). This is the same group of patients as FAS

The end of study status will be summarized for FAS by:

- Number and percentage of patients who completed the 24-Months follow-up period
- Number and percentage of patients who early discontinued the study (overall and by primary reason)

The end of treatment status will be summarized for FAS overall and independently for each of the end of study status groups by:

- Number and percentage of treated patients who completed study treatment (overall and by reason)
- Number and percentage of treated patients who permanently discontinued the study treatment (overall and by primary reason)

Length of follow-up, defined as date of last contact – study treatment start date + 1 will be reported for FAS overall and by end of study status.

Disposition of patients by expected follow-up visit attendance will also be presented for each of the expected visit schedule as defined in IAP Section 9.5.

Disposition of patients will be presented overall and by Country and Site level.

All disposition information described above will be listed, including relevant disposition dates (informed consent date, follow-up visit dates, date of last contact). A separate listing with death details will also be presented (date of death, primary reason for dead and autopsy details if available).

10.2 Protocol Deviations/Exclusion from Analysis Populations

10.2.1 Important Protocol Deviations

Important protocol deviations (IPDs) are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being. Since this is a non-interventional study and all procedures will be performed as per clinical practice, deviation from the expected schedule of assessments as presented in the Protocol Section 9.2.4 are not considered IPDs.

The list of potential protocol deviations is available at Appendix 18.1 according to the study Protocol Deviation Plan version 1.0 from 21 November 2019.

A frequency table with all IPDs based on FAS will be presented.

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

This study only considers one analysis population (FAS). The only reason for not being included in FAS is by not receiving a cladribine dose although there is a prescription for it as per the study inclusion criterion 4 as defined in Protocol Section 9.2.1. This will be summarized in the disposition table as defined in IAP Section 10.1.

11 Demographics and Other Baseline Characteristics

If not stated otherwise, the following analyses will be performed based on the FAS.

11.1 Demographics

Demographic characteristics and physical measurements will be summarized descriptively using the following information from the baseline visit eCRF pages.

The following demographic characteristics will be included:

- Sex: Male, Female
- Race: Caucasian, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Pacific Islander, Other, not collected due to local regulations
- Age (years) at informed consent
- Age categories:
    - <65 years
    - ≥65 years
        - 65-74
        - 75-84
        - ≥85 years
- Country

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version at the time of database lock, preferred term as event category and system organ class (SOC) body term as body system category. Each participant will be counted only once within each preferred term (PT) or SOC.

Medical history will be displayed in terms of frequency tables by six main categories as collected in the eCRF: any medical history, Relapsing-Remitting Multiple Sclerosis (RRMS) related medical history, ongoing medical history (severe/moderate/mild). Under each category, frequencies will be displayed by condition type (Malignancy, Severe Opportunistic Infection and Other relevant conditions) and under each condition type by primary SOC and PT in alphabetical order.

A listing will also be presented with all conditions reported.

11.3 Other Baseline Characteristics

11.3.1 Disease Characteristics

Information on disease characteristics collected at baseline will be summarized. Summary statistics will be presented for:

- Disease duration (Months) = (ICF date – Initial MS diagnosis date +1)
- Reason for switching to Cladribine treatment
- Baseline Magnetic Resonance Imaging (MRI) results:
    - Time since last MRI defined as ICF date – Date of last MRI scan + 1
    - Total number of T1 Gd+ lesions
    - Total number of T2 lesions
    - Total Number of CUA Lesions

A Listing will be presented with all disease characteristics.

11.3.2 Previous MS medication history

11.3.2.1 Previous DMD history

Information on the most recent previous DMD medication will be summarized as number and percentage of patients under each specific DMD as collected in eCRF MS Medication History and grouped as described in IAP Section 8.2. For each DMD, treatment duration and reason for switching to Cladribine treatment will be described.

A listing will be created with most recent previous DMD medication, including the DMD name, start date, stop date and reason for switching to Cladribine treatment.

11.3.2.2 Immunosuppressive/immunomodulatory agents history

The number and percentage of patients who have ever been treated with immunosuppressive/immunomodulatory agents will be described, overall and by treatment status at baseline (ongoing and previous immunosuppressive/immunomodulatory). For those who have a history of previous immunosuppressive/immunomodulatory agents, the number and percentage of patients under each preferred name of the specific reported agent(s) coded using the most recent World Health Organization Drug Dictionary (WHO-DD) and the treatment duration will be reported. Treatment duration (Months) will be calculated as treatment stop date – treatment start date +1 for previous medications and ICF date – treatment start date +1 for ongoing medications.

All reported previous immunosuppressive/immunomodulatory agents will be listed.

12 CMs/Procedures

The following analyses will be performed based on the FAS.

CMs are medications, other than study treatment, which are taken by patients any time during the on-treatment period.

Previous medications are medications, other than study treatment and pre-medications for study treatments, which started before the first administration of study treatments.

A medication may be classified as both concomitant and previous. The respective flags will be derived based on the start date as per the rules specified in IAP Section 9.8.2.

Concomitant and previous treatment each will be summarized by number and percentage of patients from the "CMs Details" CRF. Anatomical Therapeutic Chemical classification (ATC)-2nd level and preferred term will be tabulated as given from the WHO-DD most current version. If any previous or concomitant medication is classified into multiple ATC classes, the medication will be summarized separately under each of these ATC classes. The summary tables will be sorted by decreasing frequency of drug class and decreasing frequency of drug name in a given drug class. In case of equal frequency regarding drug class (respectively drug name), alphabetical order will be used. In case any specific medication does not have an ATC classification level 2 coded term, it will be summarized under "Unavailable ATC classification" category. Each participant will only be counted once, even if he/she received the same medication at different times.

All **concurrent procedures**, which were undertaken during the on-treatment period will be summarized according to the CRF page "Concomitant Procedures". Concurrent procedures will be MedDRA coded. Number and percentage of patients with concurrent procedures (Prior, on or after the first day of study treatment) overall and by type of procedure (as classified by medical review) will be presented.

Two separate listings will be created, one including all medications reported and other for all procedures reported.

13 Study Treatment: Adherence and Exposure

The following analyses will be performed based on the FAS. All dosing calculations and summaries will be based on "Cladribine Administration" CRFs pages.

Cladribine is administered in the first 2 weeks of each the 2 years of treatment planned. Therefore, it is not accurate to report treatment duration based on the date of last cladribine administration. Cladribine treatment exposure will then be summarized as number and percentage of patients who completed the treatment overall and for each of the 4 treatment courses (Year 1: Week 1, Year 1: Week 2, Year 2: Week 1 and Year 2: Week 2). Overall and for each treatment course, the number and percentage of patients with dose delays or dose changes will be reported, including the associated reasons. Number and percentage of patients who permanently discontinued the treatment and associated reasons for discontinuation will also be reported.

Cladribine utilization and adherence will be summarized for each treatment course (Year 1: Week 1, Year 1: Week 2, Year 2: Week 1 and Year 2: Week 2) and overall. For each treatment course, the following information will be presented:

- Dose, calculated as Number of tablets taken × 10/Weight (kg) at time of prescription
- Number of tablets prescribed
- Number of tablets taken
- Adherence to treatment, calculated as 100 × Taken tablets/Prescribed tablets. Adherence will also be presented under the following categories
    - <60%
    - [60%-80%]
    - [80%-90%]
    - [90%-100%]

For the overall summary, the cumulative dose will be presented instead of dose. The cumulative dose will be calculated as the sum of all doses from all available treatment courses prior to treatment discontinuation or end of the 2 years treatment period.

14 Effectiveness Analyses

The following analyses will be performed based on the FAS except when otherwise stated.

14.1 Primary Outcome ARR

The primary outcome for this study is the difference in ARR between the pre-baseline 12-month period and over the 12 months period before the End of Study follow-up (2 years).

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

14.1.1 Primary Objective: Derivation and analysis of the Primary Outcome ARR

Derivations

Pre-baseline ARR will be defined as a total number of relapses reported in the last 12 months prior to Cladribine treatment as collected in the "12 Month Historical MS Data".

Twelve month period before the End of Study follow-up (2 years) ARR will be calculated as the sum of the number of MS relapses reported at Visit 3 and Visit 4 divided by the number of days between Visit 4 date and Visit 2 date and multiplied by 365.25. If a patient discontinues the study prior to Visit 4, it will be set to missing and excluded from the primary analysis.

For other study visits, ARR will be calculated similarly including data from the last 2 visits, except for ARR at Visit 1 for which only the last 6-month data will be included, and the annualized rate will be adjusted as per the formula described above. For ARR at Visit 1 and Visit 2, Cladribine start date will be used as the date to calculate the number of days elapsed.

Analysis methods

No missing data imputation will be performed. Patients with missing data at one or both time points will not be included in the analysis. A one-way Repeated Measures Analysis of Variance (ANOVA) will be used to compare the differences between pre and post-baseline ARR if the data is normally distributed. The two-tailed test hypothesis for the primary outcome is H_0: ARR mean difference between pre and post-baseline ARR is 0 vs H_1: ARR mean difference between pre and post-baseline is different than 0. Statistical significance will be assessed at the 5% level.

In case the data is not normally distributed, Wilcoxon signed-rank test will be used instead. The Shapiro-Wilk test will be used to test for data normality.

Main primary outcome table will include only summary statistics for pre-baseline and post-baseline ARR data including the p-value for the statistical test result described above. Additionally, a table includes ARR summary statistics by visit, including ARR at each visit and absolute and relative change from baseline. For a change from baseline, 95% CIs for the difference will be presented together with summary statistics. These CIs will be included as a descriptive measure of effect and no inferences will be made.

14.1.2 Sensitivity Analyses of the Primary Outcome ARR

A sensitivity analysis will be conducted using two different methods for missing data imputation, to assess the robustness of the primary analysis described above.

The first method will include a Last Observation Carried Forward (LOCF) approach, for which the last available ARR from previous visits will be used for the analysis.

The second method will include a Baseline Observation Carried Forward (BOCF) for which missing data for post-baseline ARR will be imputed as the pre-baseline ARR.

Both summary statistics and statistical results will be presented in the same table as the primary analysis. These sensitivity analyses are considered as supportive of the primary analysis.

14.1.3 Subgroup Analyses of the Primary Outcome ARR

The subgroup analyses will be performed on the primary endpoint assessment based on the FAS for all subgroup levels defined in IAP Section 8.2 "Subgroup definition and parametrization". All the subgroup analyses are exploratory and will be performed unstratified. No adjustment for multiplicity will be performed. Sensitivity analysis will not be performed in the subgroup analysis.

A forest plot will be presented with the 95% CIs for the difference in ARR between pre and post-baseline for each subgroup for the analysis of the primary outcome. A line plot by subgroup with ARR over time (from Baseline to Visit 4) with means and 95% CIs for ARR at each visit will be presented.

14.2 Secondary Outcome ARR

One of the secondary outcomes for this study is the difference in ARR between the pre-baseline 12-month period and over the 12 months period after the start of cladribine (1 year)

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

14.2.1 Secondary Objective: Derivation and analysis of the Secondary Outcome ARR

Derivations

Pre-baseline ARR will be defined as the total number of relapses reported in the last 12 months prior to Cladribine treatment as collected in the "12 Month Historical MS Data".

Twelve month period after the start of Cladribine treatment ARR will be calculated as the sum of the number of MS relapses from Visit 1 and Visit 2 divided by the number of days between Visit 2 data and start date of Cladribine and multiplied by 365.25. If a patient discontinues the study prior to Visit 2, it will be set to missing and excluded from the primary analysis.

Analysis methods

No missing data imputation will be performed. Patients with missing data at one or both time points will not be included in the analysis. A one-way Repeated Measures ANOVA will be used to compare the differences between pre and post-baseline ARR if the data is normally distributed. The two-tailed test hypothesis for the primary outcome is H_0: ARR mean difference between pre and post-baseline ARR is 0 vs H_1: ARR mean difference between pre and post-baseline is different than 0. Statistical significance will be assessed at the 5% level.

In case the data is not normally distributed, Wilcoxon signed-rank test will be used instead. The Shapiro-Wilk test will be used to test for data normality.

14.2.2 Sensitivity Analyses of the Secondary Outcome ARR

No sensitivity analysis will be performed on the secondary outcome analysis.

14.2.3 Subgroup Analyses of the Secondary Outcome ARR

The subgroup analyses will be performed on the secondary outcome assessment based on the FAS for all subgroup levels defined in IAP Section 8.2 "Subgroup definition and parametrization". All the subgroup analyses are exploratory and will be performed unstratified. No adjustment for multiplicity will be performed.

A forest plot will be presented with the 95% CIs for each subgroup for the analysis of the secondary outcome.

14.3 Secondary Outcome 6-month Disability Progression

The percentage of patients with 6-month disability progression at the end of the study follow-up period (2 years), measured as EDSS, timed 25-foot walk (T25FW) (optional) and 9-hole peg test (9-HPT) (optional) is a secondary outcome of this study.

Disability progression is defined as progression on ≥1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ≥24 weeks apart and with a ≥20% minimum threshold change for T25FW and 9HPT. Progression on EDSS is defined as at least 1 point in the EDSS score or an increase of at least 1.5 points if the baseline EDSS score is 0.

14.3.1 Secondary Objective: Derivation and analysis of the Secondary Outcome 6-month Disability Progression

Derivations

Disability progression will be assessed using the Visit 4 data and comparing the results with Visit 3. As per definition, if Visit 4 and Visit 3 dates are not separated by at least 24 weeks, disability progression will be set to missing. Disability progression will be assessed if at least one assessment (EDSS, T25FW or 9HPT) is available. As per definition, disability progression will be derived as "Yes" if at least one of the below cases occur:

- Visit 4 EDSS is ≥1 point greater than Visit 3 EDSS if Visit 3 EDSS is greater than 0;
- Visit 4 EDSS is 1.5 or greater when Visit 3 EDSS is 0;
- 20% increase in the T25FW score (average of the two trials) from Visit 3 to Visit 4;
- 20% increase in the 9HPT score (The two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the two reciprocals are averaged) from Visit 3 to Visit 4.

If none of those cases occurred, disability progression will be set to "No".

Analysis methods

No missing data imputation will be performed. The proportion of patients with 6-month disability progression at the end of study will be presented including associated 95% Clopper Pearson exact intervals.

Disability progression at Visit 1, Visit 2 and Visit 3 will also be presented and derived in the same way. A bar plot with disability progression from Visit 1 to Visit 4 will be presented. Additionally, the results for EDSS, 9HPT and T25FW scores will be presented descriptively by Visit, including an absolute and relative change from baseline and to the previous visit.

14.3.2 Sensitivity Analyses of the Secondary Outcome 6-month Disability Progression

Four sensitivity analyses will be performed to assess the robustness of the results of the secondary outcome.

The first sensitivity analysis will be a complete case analysis that will derive disability progression only for cases where it can be determined without reservations, setting all the other cases to missing. This means that if only one or two out of the three assessments are available, disability progression will either be "Yes" if those are sufficient for the assessment or "Missing" if progression criteria are not observed in any of the available assessments. The number of patients included in these analyses will be less than the ones includes in the main analysis.

The second sensitivity analysis will include a Non-responder (NR) missing data imputation. All patients for which disability progression cannot be assessed or is "No" but not all three assessments are available will be set to "Yes".

Both approaches will provide a significant underestimation of the treatment effect due to the anticipated missing data in the optional assessments.

A third sensitivity analysis will be performed using EDSS only for disability assessment derivation.

The fourth sensitivity analysis will replicate the above described third sensitivity analysis but by two subgroups:

- Patients with at least one EDSS score obtained within 3 months following a relapse
- Patients with both EDSS scores obtained more than 3 months following a relapse

14.3.3 Subgroup Analyses of the Secondary Outcome 6-month Disability Progression

The subgroup analyses will be performed on the secondary outcome assessment based on the FAS for all subgroup levels defined in IAP Section 8.2 "Subgroup definition and parametrization". All the subgroup analyses are exploratory and will be performed unstratified.

A bar plot with disability progression from Visit 1 to Visit 4 overall and by subgroup will be presented.

14.4 Secondary Outcome 6-month Disability Improvement

The percentage of patients with 6-month disability improvement at the end of the study follow-up period (2 years), measured as EDSS, T25FW (optional) and 9-HPT (optional).

Disability Improvement is defined as an improvement on ≥1 of 3 components (EDSS, T25FW, and/or 9HPT) confirmed ≥24 weeks apart and with a ≥20% minimum threshold change for T25FW and 9HPT. Improvement on EDSS is defined as a decrease in EDSS by at least 1 point (1.5 points if baseline EDSS was 1.5).

14.4.1 Secondary Objective: Derivation and analysis of the Secondary Outcome 6-month Disability Improvement

Derivations

Disability improvement will be assessed using the Visit 4 data and comparing the results with Visit 3. As per definition, if Visit 4 and Visit 3 dates are not separated by at least 24 weeks, disability improvement will be set to missing. Disability improvement will be assessed if at least one assessment (EDSS, T25FW or 9HPT) is available. As per definition, disability improvement will be derived as "Yes" if at least one of the below cases occur:

- Visit 4 EDSS is ≥1 point smaller than Visit 3 EDSS if Visit 3 EDSS is greater than 1.5;
- Visit 4 EDSS is 0 when Visit 3 EDSS is 1.5;
- 20% decrease in the T25FW score (average of the two trials) from Visit 3 to Visit 4;
- 20% decrease in the 9HPT score (The two trials for each hand are averaged, converted to the reciprocals of the mean times for each hand and then the two reciprocals are averaged) from Visit 3 to Visit 4.

If none of those cases occurred, disability improvement will be set to "No".

Analysis methods

No missing data imputation will be performed. The proportion of patients with 6-month disability improvement at the end of study will be presented including associated 95% Clopper Pearson exact intervals. Disability improvement at Visit 2 and Visit 3 will also be presented and derived in the same way as described for Visit 4.

14.4.2 Sensitivity Analyses of the Secondary Outcome 6-month Disability Improvement

Four sensitivity analyses will be performed to assess the robustness of the results of the secondary outcome 6-month disability improvement.

The first sensitivity analysis will be a complete case analysis that will derive disability improvement only for cases where it can be determined without reservations, setting all the other cases to missing. This means that if only one or two out of the three assessments are available, disability improvement will either be "Yes" if those are sufficient for the assessment or "Missing" if improvement criteria are not observed in any of the available assessments. The number of patients included in these analyses will be less than the ones includes in the main analysis.

The second sensitivity analysis will include an NR missing data imputation. All patients for which disability improvement cannot be assessed or is "No" but not all three assessments are available will be set to "No".

In this case, it is expected that the complete cases approach will overestimate the true treatment effect while the NR will provide an underestimation of the true treatment effect.

A third sensitivity analysis will be performed using EDSS only for disability assessment derivation.

The fourth sensitivity analysis will replicate the above described third sensitivity analysis but by two subgroups:

- Patients with at least one EDSS score obtained within 3 months following a relapse
- Patients with both EDSS scores obtained more than 3 months following a relapse

14.4.3 Subgroup Analyses of the Secondary Outcome 6-month Disability Improvement

The subgroup analyses will be performed on the secondary outcome assessment based on the FAS for all subgroup levels defined in IAP Section 8.2 "Subgroup definition and parametrization". All the subgroup analyses are exploratory and will be performed unstratified.

A bar plot with disability improvement from Visit 1 to Visit 4 overall and by subgroup will be presented.

15 Safety Analyses

Safety analyses will be done on the FAS.

15.1 Adverse Events

The TEAE are those events with onset dates occurring within the on-treatment periods as defined in Section 9.7.

The AEs related to study treatment are those events with relationship missing or "Related".

All analyses described in Section 15.1 will be based on TEAEs if not otherwise specified. The AE listings will include all AEs (whether treatment-emergent or not). AEs outside the on-treatment period will be flagged in the listings.

Unless otherwise specified, TEAEs will be summarized by number and percentage of patients with the TEAE in the category of interest, primary SOC and PT in decreasing frequency.

Each participant will be counted only once within each SOC or PT. If a participant experiences more than one AE within a SOC or PT for the same summary period, only the AE with the strongest relationship or the worst severity, as appropriate, will be included in the summaries of relationship and severity.

15.1.1 All Adverse Events

The AEs will be summarized using the latest version of MedDRA PT as event category and MedDRA primary SOC body term as body system category.

Incomplete AE-related dates will be handled as specified in Section 9.8.1.

The following tables will be created

- TEAE summary table with the number and percentage of patients having:
    - TEAE
    - TEAE of Special Interest (TEAESI)
    - TEAE leading to death
    - TEAE leading to Cladribine dose reduction
    - TEAE leading to Cladribine temporary discontinuation
    - TEAE leading to Cladribine permanent discontinuation
    - TEAE leading to study termination
    - TEAE not recovered/resolved
    - Any serious TEAE:
        - TEAESI
        - Leading to death
        - Leading to Cladribine dose reduction

        - Leading to Cladribine temporary discontinuation
        - Leading to Cladribine permanent discontinuation
        - Leading to study termination
        - Not recovered/resolved
    - Cladribine related TEAE:
        - TEAESI
        - Serious
        - Leading to death
        - Leading to Cladribine dose reduction
        - Leading to Cladribine temporary discontinuation
        - Leading to Cladribine permanent discontinuation
        - Leading to study termination
        - Not recovered/resolved

- Incidence of TEAE by Primary SOC and PT
- Incidence of Serious TEAE by Primary SOC and PT
- Incidence of Serious TEAE related to Cladribine by Primary SOC and PT
- Incidence of TEAE leading to Cladribine temporary discontinuation Primary SOC and PT
- Incidence of related TEAE leading to Cladribine temporary discontinuation Primary SOC and PT
- Incidence of TEAE leading to Cladribine permanent discontinuation Primary SOC and PT
- Incidence of related TEAE leading to Cladribine permanent discontinuation Primary SOC and PT
- Incidence of TEAE leading to death by Primary SOC and PT
- Incidence of related TEAE leading to death by Primary SOC and PT
- Incidence of TEAE by Primary SOC and PT and relationship to Cladribine
- Incidence of TEAE by Primary SOC and PT and severity
- Incidence of TEAESI by Primary SOC and PT and severity
- Incidence of TEAESI by Primary SOC and PT and by relationship to Cladribine

- Incidence of Serious TEAESI by Primary SOC and PT and by relationship to Cladribine

All AEs regardless of being treatment-emergent or not will be listed.

15.1.2 Adverse Events Leading to Discontinuation of Study Treatment

The frequency (number and percentage) of patients with TEAE leading to temporary or permanent Cladribine discontinuation will be presented in the TEAE summary table. Summaries by SOC and PT will also be presented with TEAE and related TEAE that led to temporary and permanent Cladribine discontinuation as described in the previous section.

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

All TEAE that led to death will be presented descriptively as explained in other sections.

A Listing with death details, including date of death, the primary reason of death and autopsy results if available will be created. Additionally, the number of linked serious adverse event (SAE) will be provided. Details on the SAE narrative will be presented in SAE narratives listing.

15.2.2 Serious Adverse Events

The following overall frequency tables will be prepared for SAEs:

- Incidence of serious AEs by SOC and PT
- Incidence of related serious AEs by SOC and PT

Separate Listings including only SAEs will be presented, including SAE criteria met and narratives of SAEs.

16 Analyses of Other Outcomes

16.1 Patient Reported Outcome MSIS29

16.1.1 Patient Reported Outcome MSIS29: Derivation and analysis of the Patient Reported Outcome MSIS29

Derivations

MSIS-29 has two available scores: physical and psychological score. Derivation of both scores from the questionnaire is presented at IAP Section 9.9.1.

Analysis methods

No missing data imputation will be performed. Summary statistics will be provided for each score independently by visit (Baseline, Visit 2 and Visit 4). For Visit 2 and Visit 4 scores, only measurements collected within the period of ± 30 days as compared to the predicted schedule will be considered for analysis. Measurements obtained outside this window will be set to missing. For post-baseline visits, absolute and relative change from baseline will be summarized, including 95% CIs for the difference between each visit scores and baseline score.

16.2 Patient Reported Outcome TSQM v1.4

16.2.1 Patient Reported Outcome TSQM v1.4: Derivation and analysis of the Patient Reported Outcome TSQM v1.4

Derivations

TSQM v1.4 has four Specific Domains (Global Satisfaction, Effectiveness, Side Effects and Convenience). Details on how to derive these components are presented at IAP Section 9.9.2.

Analysis methods

No missing data imputation will be performed. Summary statistics will be provided for each domain independently by visit (Visit 1, Visit 2, Visit 3 and Visit 4). For Visit 1, Visit 2, Visit 3 and Visit 4 scores, only measurements collected within the period of ± 30 days as compared to the predicted schedule will be considered for analysis. Measurements obtained outside this window will be set to missing. For post Visit 2, Visit 3 and Visit 4, absolute and relative change from the last visit will be summarized, including 95% CIs for the difference between each visit scores and baseline score.

CCI [redacted]

[redacted]

Derivations

CCI [redacted]

CCI [redacted]

[redacted]

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

16.4 Other Outcome MRI Lesions

16.4.1 Other Outcome MRI Lesions: Derivation and analysis of the Other Outcome MRI Lesions

Derivations

No derivations will be performed on this outcome. Data reported on "MRI and Relapse Count" and "12 Month Historical MS Data" CRF pages will be reported as collected.

Analysis methods

No missing data imputation will be performed. Summary statistics will be provided for each score independently by visit (Baseline, Visit 1, Visit 2, Visit 3 and Visit 4). For post-baseline visits,

absolute and relative change from baseline will be summarized, including 95% CIs for the difference between each visit scores and baseline score.

17 References

IQVIA. (2019, November 14). Treatment Satisfaction Questionnaire for Medication (TSQM) User Manual. *TSQM Manual*. IQVIA.

RIMS - Rehabilitation in Multiple Sclerosis. (n.d.). *EURIMS*. Retrieved from EURIMS: https://www.eurims.org/E-education/multiple-sclerosis-impact-scale-29-items.html

18 Appendix

18.1 List of Potential Protocol Deviations

Identification of PD		
Categories	**Short Description**	**Source / Method of Identification**
1-Informed Consent Criteria	Non-compliance in relation to Informed Consent Process (e.g.- ICF Not signed ICF wrong version signed ICF completed incorrectly Patient not re-consented)	Manually-identified Remote/ On Site Monitoring Visits
2- Eligibility and Entry Criteria	Non-compliance in relation to inclusion/exclusion criteria (e.g.- Patient enrolled without meeting one or more inclusion criteria)	Manually-identified Remote/ On Site Monitoring Visits
6- Serious Adverse Event Criteria	Non-compliance in relation to safety reporting (ADR/ AESI/SAE/ Pregnancy or lactation/ Parent – Child Fetus report Form/ reported late (as per protocol) or not reported at all)	Manually-identified Remote/ On Site Monitoring Visits
12. Source documents criteria	Non-compliance in relation to source documents (e.g., data are entered in Electronic Data Capture [EDC] but source data are not available for patient)	Manually-identified Remote/ On Site Monitoring Visits
13- Regulatory or Ethics Approvals Criteria	Non-compliance in relation to RA, EC approvals (e.g.- EC / RA Approval or annual renewal not in place)	Manually-identified Remote/ On Site Monitoring Visits

18.2 List of Interim Analysis Outputs

Output Number	Output Title
Table 15.1.1.1	Subject Disposition Status
Table 15.1.4.1	Demographic Characteristics – FAS Analysis Set
Table 15.1.6.1	Disease History − FAS Analysis Set
Table 15.1.6.3	Immunosuppressive/immunomodulatory history
Table 15.2.2.1.1	ARR comparison between Baseline and 12-Months after start Cladribine treatment – FAS Analysis Set
Table 15.2.2.2	ARR comparison between Baseline and 12-Months after start Cladribine treatment by Baseline DMD treatment – FAS Analysis Set
Figure 15.2.2.1	Forest Plot of ARR comparison between Baseline and 12-Months after start Cladribine treatment by Baseline DMD – FAS Analysis Set
Table 15.2.3.2	6-Month Disability Progression at Visit 1 (6-Months Follow-up), Visit 2 (12-Months Follow-up) and Visit 3 (18-Months Follow-up) – FAS Analysis Set *(Limited to Visit 2)*
Table 15.2.3.5	6-Month Disability Progression at Visit 1 (6-Months Follow-up), Visit 2 (12-Months Follow-up) and Visit 3 (18-Months Follow-up) by Baseline DMD treatment – FAS Analysis Set *(Limited to Visit 2)*
Figure 15.2.3.1	Bar Plot of 6-Month Disability Progression by Visit (Overall and by Baseline DMD) – FAS Analysis Set *(Limited to Visit 2)*
Table 15.2.4.2	6-Month Disability Improvement at Visit 1 (6-Months Follow-up), Visit 2 (12-Months Follow-up) and Visit 3 (18-Months Follow-up) – FAS Analysis Set *(Limited to Visit 2)*
Table 15.2.4.4	6-Month Disability Improvement at Visit 1 (6-Months Follow-up), Visit 2 (12-Months Follow-up) and Visit 3 (18-Months Follow-up) by Baseline DMD treatment – FAS Analysis Set *(Limited to Visit 2)*
Figure 15.2.4.1	Bar Plot of 6-Month Disability Improvement by Visit (Overall and by Baseline DMD) – FAS Analysis Set *(Limited to Visit 2)*
Table 15.2.5.1	MSIS29 results by Visit – FAS Analysis Set
Table 15.2.6.1	TSQM v1.4 results by Visit – FAS Analysis Set
Table 15.2.7.1	CCI [redacted]
Table 15.3.1.1	Overview of Treatment-Emergent Adverse Events (TEAEs) – FAS Analysis Set
Table 15.3.1.2	TEAE by Primary System Organ Class (SOC) and Preferred Term (PT) – FAS Analysis Set
Table 15.3.1.3	Serious TEAE by Primary System Organ Class (SOC) and Preferred Term (PT) – FAS Analysis Set
Table 15.3.1.7	TEAE leading to Cladribine Permanent Discontinuation by Primary System Organ Class (SOC) and Preferred Term (PT) – FAS Analysis Set
Table 15.3.1.9	TEAE leading to death by Primary System Organ Class (SOC) and Preferred Term (PT) – FAS Analysis Set
Table 15.3.1.11	TEAE by Primary System Organ Class (SOC) and Preferred Term (PT) by relationship to Cladribine – FAS Analysis Set

Table 15.3.1.13	TEAESI by Primary System Organ Class (SOC) and Preferred Term (PT) – FAS Analysis Set
Listing 16.2.1.1	Consented/Enrolled Subjects
Listing 16.2.1.2	Disposition by Visit – FAS Analysis Set
Listing 16.2.1.3	Discontinued Subjects – FAS Analysis Set
Listing 16.2.1.5	Demographic characteristics – FAS Analysis Set
Listing 16.2.1.7	Disease History – FAS Analysis Set
Listing 16.2.1.8	Previous Disease Modifying Drug (DMD) history – FAS Analysis Set
Listing 16.2.1.9	Previous Immunosuppressive/immunomodulatory history – FAS Analysis Set
Listing 16.2.2.1	Relapse Count – FAS Analysis Set
Listing 16.2.2.2	Expanded Disability Status Scale (EDSS) – FAS Analysis Set
Listing 16.2.2.5	Multiple Sclerosis Impact Scale (MSIS-29) – FAS Analysis Set
Listing 16.2.2.6	Treatment Satisfaction Questionnaire for Medication (TSQM v1.4) – FAS Analysis Set
Listing 16.2.2.7	CCI [redacted]
Listing 16.2.3.1	Adverse Events I – FAS Analysis Set
Listing 16.2.3.2	Adverse Events II – FAS Analysis Set
Listing 16.2.3.3	Adverse Events III – FAS Analysis Set
Listing 16.2.3.9	Listing of Deaths – FAS Analysis Set

Electronic Signature Manifestation

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

Signer Full Name	Meaning of Signature	Date and Time
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	19 Nov 2021 08:00:39 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	19 Nov 2021 08:18:07 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	19 Nov 2021 09:18:57 UTC
	Document Approval (I certify that I have the education, training and experience to perform this task)	23 Nov 2021 02:36:48 UTC