Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS700568_0078
Title	CLadribine tablets: Observational evaluation of effectIveness and patient-reported outcomes (PROs) in suboptimally Controlled patients previously taKing injectable disease-modifying drugs (DMDs) for relapsing forms of Multiple Sclerosis (RMS) (CLICK-MS)
Study Phase	Phase IV study
Investigational Medicinal Product(s)	Cladribine
Clinical Study Protocol Version	14 February 2024 / Version 7.0
Replaces Version	1 July 2022 / Version 6.0
Integrated Analysis Plan Author	**Coordinating Author** PPD , EMD Serono PPD **Author** PPD PPD
Integrated Analysis Plan Date and Version	30 April 2024 / Version 4.0
Replaces Version	08 February 2023 / Version 3.0
Integrated Analysis Plan Reviewers	**Function** **Name** PPD PPD PPD PPD

Approval Page

Integrated Analysis Plan: MS700568_0078

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Signature: Date:

Integrated Analysis Plan Sponsor Coordinating Author

EMD Sereno, Inc (a subsidiary of Merck KGaA, Darmstadt, Germany)

Approval of the Integrated Analysis Plan (IAP) by all EMD Serono Data Analysis Responsible has to be documented within ELDORADO via eSignature. With the approval within ELDORADO, the EMD Serono responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

1 Table of Contents

2 List of Abbreviations and Definition of Terms

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALC	Absolute Lymphocyte Count
ARR	Annualized Relapse Rate
aSPMS	active Secondary Progressive Multiple Sclerosis
ATC	Anatomical Therapeutic Chemical Classification
BDI-FS	Beck-Depression Inventory - Fast Screen
BMI	Body Mass Index
CI	Confidence Interval
CIS	Clinically Isolated Syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Event
CU	Combined Unique
DMD	Disease-Modifying Drug
eCRF	Electronic Case Report Form
ePRO	Electronic Patient-Reported Outcome
FAS	Full Analysis Set
Gd+	Gadolinium-Enhancing
GENMOD	Generalized Linear Model
HIV	Human Immunodeficiency Virus
IAP	Integrated Analysis Plan
JCV	John Cunningham Virus
KM	Kaplan-Meier
MCS	Mental Component Summary Score
MedDRA	Medical Dictionary for Regulatory Activities
MH	Mental Health
MFIS-5	Modified Fatigue Impact Scale – 5-Item Version
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis

MS-TAQ	Multiple Sclerosis Treatment Adherence Questionnaire
NB	Negative Binomial
PCS	Physical Components Summary Score
PDDS	Patient Determined Disease Steps
PF	Physical Function
PP	Per Protocol Analysis Set
PPMS	Primary Progressive Multiple Sclerosis
PRO	Patient-Reported Outcomes
PT	Preferred Term
RMS	Relapsing form of Multiple Sclerosis
RRMS	Relapsing-Remitting Multiple Sclerosis
SAE	Serious Adverse Events
SAF	Safety Analysis Set
SAS	Statistical Analysis System
SD	Standard Deviation
SF	Short Form Health Survey
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Events
TSQM	Treatment Satisfaction Questionnaire for Medication
USPI	United States Product Information
WHO-DD	WHO-Drug Dictionary
WPAI-MS	Work Productivity Activity Impairment – MS

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	11 July 2019	PPD	Not Applicable
2.0 Draft	07 April 2020	PPD	Updated for the use of the Optum software for the derivation of the composite scores of the SF36 questionnaire Updated to replace 'enrolment visit' with 'baseline visit' Time window for MS-TAQ questionnaire during the study updated from ±30 days to ±15 days Section 14.1.1 updated to highlight that the last available date of a patient will be used in the Interim Analyses to determine the Time on Study and ARR Updated to use the correct version of the SF 36 questionnaire Updated section 9, General Specifications for Data Analyses, to take into account the Handling of partially missing dates Updated section 13 giving a definition of treatment compliance Section 14.1.4: the description of the multiple imputation analysis of the primary endpoint has been extended
2.0 Final	08 February 2022	PPD	Updated after CTP amendment 7.0 to: - Analyze the 2-year Safety extension period. Throughout the document, months "48" and "48/54" both refer to the original 24-month study plus the 24-month Safety extension - Nomenclature updated per CTP amendment: "Subject" replaced by "Patient"
3.0 Final	08 February 2023	PPD	Section 6.6 update to clarify which is the first day of the safety extension period and to clarify that only patients who started the Year 2 treatment will be included in the safety extension analysis. Section 8.2 updated to clarify the definition of the Per Protocol Analysis Set and the Safety Extension Analysis Set (MRI removed from the derivation). Section 9 updated to remove the analysis window for exposure data, PDDS and MS-TAQ. The definition of the analysis window

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
			for the other PROs has been updated to consider the correct months. Section 9 updated to ensure that the imputation of the partial date for the last DMD is always before the date of first dose of cladribine. In Section 9 the following sentence has been removed since it is not related to specifications for the analysis: 'the last assessment of the safety extension, Visit 10, will be considered missing if not recorded within 30 days of the last planned assessment.' Section 10.1 updated to clarify that the number of patients included in the SAFX will be presented. Section 13 updated by adding the definition for the date of discontinuation of cladribine tablets. In Section 14.2 the analysis of MRI data during the safety extension period has been removed.
4.0 Final	xx xxx 2024	PPD	Removed 2-year safety extension related texts from abbreviations, paragraphs, tables, footnotes, and affiliated data collection items and timepoints. The updated sections are as follows: Sections 2, 4, 5, 6, 6.6 (sections removed), 8.2, 13, 14.2, 15, 15.1 and 16.3

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 analysis and interim analyses, of data collected for protocol MS700568_0078. 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 based upon section 9.7 (Data Analysis) of the study protocol and protocol amendments and is prepared in compliance with International Conference on Harmonization (ICH) E9. It describes analyses planned in the protocol and protocol amendments.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
Primary			
To estimate the annualized relapse rate (ARR) over a 24-month period in patients with Relapsing form of Multiple Sclerosis (RMS), including relapsing-remitting multiple sclerosis (RRMS) and active secondary progressive multiple sclerosis (aSPMS), who are treated with cladribine tablets in a real-world setting and after suboptimal response to any injectable Disease-Modifying Drug (DMD) approved in the US for RMS	ARR over 24 months of treatment with cladribine tablets (prospectively collected data)	24-month period from first dose of cladribine tablets (or 30 months if Year 2 treatment is delayed)	Section 14.1
Secondary			
To assess Patient-Reported Outcomes (PROs) and treatment adherence and treatment satisfaction during treatment with cladribine tablets	Baseline scores, scores at the timepoints and change in scores from Baseline to timepoints (Month 6, 12 and 24) for the following PROs (collected via electronic PRO [ePRO] at the practice or at the patient's home): • 14-Item Treatment Satisfaction Questionnaire for Medication (TSQM) • 36-Item Short Form Health Survey (SF-36) • Modified Fatigue Impact Scale – 5-item version (MFIS-5) • Beck-Depression Inventory – Fast Screen (BDI-FS) (7 items) • Work Productivity Activity Impairment – MS (WPAI-MS) (6 items) • Patient Determined Disease Steps (PDDS) scale Treatment adherence based on modified versions of the MS-TAQ; data to be collected via ePRO at Baseline (modified Self-Injectables Version to assess adherence during last previous injectable DMD treatment, only baseline scores) and at the end of Months 1, 2, 13, and 14 (modified for cladribine tablets, only scores at the different time points)	24-month period from enrolment Timepoints for TSQM, SF-36, MFIS-5, BDI-FS, WPAI-MS and PDDS: Baseline, months 6, 12 and 24 (or 30 months if Year 2 treatment is delayed) Adherence assessment timepoints: Baseline (adherence to previous DMD), Months 1, 2, 13, 14 (adherence to cladribine)	Section 16.3 and section 16.4

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
Other relapse analyses	Proportion of patients experiencing a relapse (24-month and 12-month periods) and ARR over the 12-month period Proportion of patients with relapse associated with hospitalization and ARR associated with hospitalization Proportion of patients with relapse associated with glucocorticoid use and ARR associated with glucocorticoid use	24-month treatment period (or 30 months if Year 2 treatment is delayed) and 12-month treatment periods from first dose of cladribine tablets	Section 14.2
To assess treatment patterns (Multiple Sclerosis [MS] treatment prior to transition to cladribine tablets, since MS diagnosis, concomitant treatment for MS during the last 2 years prior to initiation of cladribine tablets (or since MS diagnosis if diagnosis <24 months), follow-up treatment in case of discontinuation of cladribine tablets)	Assessment of previous treatment for MS: • Previous DMD received for MS during the last 2 years • Number of previous DMD received for MS (a) during the last 2 years and (b) in total • Reasons for discontinuation of last previous DMD Assessment of concomitant MS medications used during the study period Proportion of patients who discontinue cladribine tablets • Reason for discontinuation of cladribine tablets • Elapsed time to discontinuation after the first dose of cladribine tablets • Number of doses and % of planned doses of cladribine tablets (as per United States Product Information [USPI]) received Subsequent treatment chosen following discontinuation of cladribine tablets	For previous treatment: 24-month period prior to initiation of cladribine tablets For concomitant medication, cladribine tablets discontinuation and subsequent treatment: 24-month period from first dose of cladribine tablets (or 30 months if Year 2 treatment is delayed)	Section 11.3 and section 12
To estimate the ARR over the 24-month period prior to initiation of cladribine tablets (or since MS diagnosis if diagnosis <24 months)	The ARR based on the last 24 months prior to the start of treatment with cladribine tablets (or since MS diagnosis if diagnosis <24 months) (retrospective data)	24-month period prior to initiation of cladribine tablets (or since MS diagnosis if diagnosis <24 months)	Section 11.3

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
To collect all serious adverse events (SAEs), adverse drug reactions (ADRs), adverse events of special interest (AESIs) and special situations during treatment with cladribine tablets over a 24-month period	SAEs, ADRs, AESIs	Adverse event (AE) collected from signed Informed Consent Form (ICF); Treatment-Emergent Adverse Events (TEAEs) considered after first treatment administration through the 24-month treatment period (or 30 months if Year 2 treatment is delayed)	Section 15
CCI			

6 Overview of Planned Analyses

There will be a baseline analysis, 3 interim analyses and a final analysis. Baseline and interim analyses are descriptive and for monitoring purposes. Multiplicity corrections will not be considered. Statistical analyses will be performed using the Electronic Case Report Form (eCRF) data gained until the cutoff dates described in the following subsections.

If the start of cladribine Year 2 treatment needs to be delayed (e.g., to allow for lymphocyte recovery to at least 800 cells per microliter), all Year 2 visits and procedures will be moved out accordingly (at most 6 months). If recovery to 800 cells/mL is not complete after the 6-month delay, Year 2 treatment should not be initiated; the patient will nonetheless be followed up until the end of the observation period.

6.1 First Interim Analysis

In the first interim analysis, safety, adherence and PRO data will be analyzed for the subset of the first 30 patients enrolled into the study after they have completed the 6-month timepoint. This analysis will be conducted primarily for evaluation of safety.

All safety data (AEs) and hematology data, including JCV status, lymphocyte subtype data, as available) will be evaluated descriptively. Treatment adherence will be evaluated on the basis of the modified versions of the MS-TAQ (at baseline modified Self-Injectables Version to assess adherence during last previous injectable DMD treatment; at Month 1 and Month 2 modified for cladribine tablets). For each PRO score (TSQM, called also TSQM-14), SF-36, MFIS-5, BDI-FS, WPAI-MS, and PDDS), the actual value at each visit and change in scores from Baseline to Month 6 will be described.

6.2 Baseline Interim Analysis

The baseline analysis will summarize the patient's baseline characteristics. It will be carried out when the baseline data collected on all patients are available.

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

6.3 Second Interim Analysis

In the second interim analysis, safety, adherence and PRO data will be analyzed as soon as 6-month data are available for all patients. This analysis will allow the interim assessment of the safety of cladribine tablets in this study.

The same endpoints as the first interim analysis will be used.

6.4 Third Interim Analysis

The third interim analysis will be performed on the 12-month data for all patients.

This analysis will include all the endpoint analyses related to the objectives of the study. For the PROs the actual value at each visit and change in scores from Baseline to Month 6 and 12 will be considered. This analysis will allow the interim assessment of all relevant aspects of the study.

6.5 Final Analysis

The final analysis will be performed on the 24-month data for all patients at the end of the study. The corresponding cutoff for the original protocol analysis is forecasted to be in June 2024.

The final analysis will include all the endpoint analyses related to the objectives of the study. For the PROs the actual value at each visit and change in scores from Baseline to Month 6, 12 and 24 will be considered. A comparison of the characteristics of patients completing the study vs. those who drop out will be conducted as well.

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the planned analyses.

8 Protocol Deviations and Analysis Populations

8.1 Definition of Protocol Deviations and Analysis Populations

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a patient's rights, safety, or well-being.

Important protocol deviations include:

- Patients that are enrolled in the study despite not satisfying the inclusion/exclusion criteria
- Patients that no longer meet the inclusion/exclusion criteria while on the study but are not withdrawn (e.g., patients may have withdrawn consent)

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

Important protocol deviations include:

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion
- The subset of these important protocol deviations that are clinically important, i.e., leading to the exclusion of a patient from an analysis population (see section 8.2)

All important protocol deviations will be documented in Standard Data Tabulation Model datasets whether identified through site monitoring, medical review or programming.

8.2 Definition of Analysis Populations and Subgroups

Full Analysis Set (FAS)

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

Per Protocol Analysis Set (PP)

The PP includes all patients who have completed a full treatment course of cladribine tablets (2 weeks of treatment [4-5 doses per week] for Years 1 and 2), according to the USPI and are compliant with all entry criteria and without protocol deviations.

If the Per Protocol analysis population includes at least 90% of patients in the FAS analysis population, additional efficacy analyses on the Per Protocol analysis population will be omitted as the differences in the results based upon these 2 analysis populations are expected to be negligible.

Safety Analysis Set (SAF)

The SAF includes all patients enrolled in the study who have received at least 1 dose of cladribine tablets (same as FAS).

Additional Subgroup Analysis Populations

	Analysis Population		
Analyses	**Full Analysis Set**	**Per Protocol Analysis Set**	**Safety Analysis Set***
Baseline Assessments (baseline characteristics of patients initiating cladribine tablets, baseline PRO data, baseline laboratory data, baseline data on previous MS DMD use, relapses during the previous 2 years [or since MS diagnosis if diagnosis <24 months], baseline MRI data, retrospective MRI data and past treatment adherence)	✓	✓	✓
Compliance and Exposure	✓		✓
Primary Endpoint Analysis (ARR over the 24-month period)	✓	✓	✓
Secondary Endpoints Analysis: The ARR over the 12-Month follow-up period , Sensitivity analyses of the ARR, ARR during the last 24 months (or since MS diagnosis if diagnosis <24 months) before starting cladribine tablets, Other relapse analyses	✓	✓	✓

	Analysis Population		
Analyses	**Full Analysis Set**	**Per Protocol Analysis Set**	**Safety Analysis Set***
Treatment patterns (MS treatment during the last 2 years (or since MS diagnosis if diagnosis <24 months) before transition to cladribine tablets, concomitant treatment for MS, follow-up treatment in case of discontinuation of cladribine tablets)	✓		✓
PROs and treatment adherence	✓		✓
Analyses of MRI imaging data	✓		✓
JCV antibody status	✓		✓
Analyses of ALC as well as complete blood count and lymphocyte subsets, if available	✓	✓	✓
Concomitant medications	✓		✓
Safety	✓		✓

Subgroup analyses will be performed for the primary endpoint on subgroups as defined below.

Subgroups:

The following subgroups will be defined:

- Patients completing the 24-month study
- Patients not completing the 24-month study (i.e., lost to follow-up, withdrawing consent, protocol deviations)
- Patients not completing treatment (i.e., completing Year 1 treatment but not Year 2 treatment, or not completing both courses of treatment each year)
- Type of MS at screening: RRMS, aSPMS, PPMS, CIS
- Patients diagnosed with MS <24 months before transitioning to cladribine tablets
- Centers
    - Pooling of centers: Because of the high number of participating centers and the anticipated small number of patients in each centers data will be pooled across centers, and the factor centers will not be considered in statistical models or for subgroup analyses.

9 General Specifications for Data Analyses

Data handling after cutoff date

Data after cutoff do not undergo the cleaning process. The only exceptions are the date of death and the date last known to be alive from the "End of Assessment Visit" in eCRF.

Data other than the date of death and the date last known to be alive obtained after the cutoff will not be displayed in any listings or used for summary statistics, e.g., laboratory values of samples taken after data cutoff, AEs with onset date after data cutoff, etc. will not be included in any analysis or listing.

Significance level

When confidence intervals (CIs) are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP. For continuous data, CIs for the mean will be calculated assuming a normal distribution of the data. CIs for binary endpoints will be presented using the Clopper-Pearson method. All statistical tests mentioned in this IAP are to be regarded as exploratory. The significance level is 5% two-sided. If p-values are to be presented for descriptive purposes it will be indicated with the statement that no inferential conclusion should be drawn from the p-value.

Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics, i.e.

- number of patients, number of patients with non-missing values, numbers of patients with missing values,
- mean, standard deviation (SD),
- median, 25th Percentile-75th Percentile (Q1-Q3),
- minimum, and maximum.

If there are no missing values this will be indicated by a 0.

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of patients of the analysis population of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits, percentages will be based on the number of patients still present in the study at that visit, unless otherwise specified.

Time to event data

Time to event data will be summarized descriptively as continuous data and using Kaplan-Meier (KM) analysis. Data summarization will include:

- Plot of KM curve with number at risk
- KM estimates with CI at fixed timepoints (e.g., every 6 months) (with number at risk/ failed)
- Median survival times with CI, and first quartile (Q1) and third quartile (Q3).

Definition of Baseline

Data entered during the baseline visit are considered baseline data for the purposes of analysis; the last value before study treatment will be considered the Baseline value. Baseline PROs can be filled out up to 7 days after the baseline visit. Baseline PRO scales will be completed before the first cladribine tablet dose is taken. Baseline MRI corresponds to the most recent MRI prior to starting cladribine tablets, which is expected to have been taken within the prior 90 days.

Definition of change from Baseline

Change from baseline = visit value – Baseline value

*Percent Change from Baseline = 100 * (visit value – Baseline value) / Baseline value*

Definition of duration

Duration will be calculated by the difference of stop and start date + 1 (if not otherwise specified).

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

Conversion factors

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

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

Handling of missing data

Unless otherwise specified, missing data will not be replaced.

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”.

Where tables are presented over time, the total of missing and non-missing observations at each timepoint should reflect the population still in the study at that time. For example, if a patient is still in the study at the timepoint but with missing data, it should be counted in the number of missing observations.

For PRO items with missing responses, the response will be managed as described in sections 16.3 and 16.4.

Handling of partially missing MS onset (first attack), MS diagnosis or prior DMD medication dates

For time since MS onset, MS diagnosis or prior DMD start dates, a missing onset day/month will be replaced by 1 for the duration derivation or the derivation of DMDs used within 24 months prior to study start. For determination of whether a DMD was used within 24 months of study start, missing ending day/month of DMD use will be replaced by the end of the month, if day is missing, or December 31, if day and month are missing. If the imputed partial dates will result in an ending date for the last DMD on or after the date of first dose for cladribine then the partial dates will be re-imputed to the date corresponding to the day before the first dose of cladribine.

Handling of partially missing dates for relapse onset and stabilization and for first attack

To identify relapses in the past 2 years a missing day/month for the onset date will be replaced by 1, while a missing ending day/month of the stabilization will be replaced by the end of the month, if day is missing, or December 31, if day and month are missing. A missing day/month of the first attack date will be replaced by 1.

Time window

Day 1 is the day of the start of study dose, the day before is Day -1 (no Day 0 is defined).

Study day / Study dose day is defined relative to Day 1.

Visits will be conducted within the context of routine clinical care; thus, the timing of study visits is approximate and not mandated by the study protocol. The PDDS and the MS-TAQ will be analyzed according to the visit collected through the eCRF. For all the other PROs collected at Months 6, 12, 24, the analysis windows are ± 1 Month (30 days). The analysis windows for the different Months will be derived considering the Day 1 (day of start of study dose), regardless of possible treatment delays at the second year. Endpoints without an analysis window will be analyzed according to the visit collected through the eCRF (if available).

Software(s)

All analyses will be performed using Statistical Analysis System (SAS)® Software version 9.4 or higher.

10 Study Patients

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

10.1 Disposition of Patients and Discontinuations

This section describes how patient disposition, study and study dose discontinuations will be summarized. The following disposition categories will be considered.

- Total number of screened patients
- Number of enrolled patients (i.e., those who gave informed consent and met all entry criteria). The corresponding percentage will be calculated using the number of screened Patients as a denominator

For the following categories, the corresponding percentage will be calculated with respect to the number of enrolled patients

- Number of patients who received at least one dose of study treatment
- Number of patients who completed the 24-month study
- Number of patients who discontinued the study treatment, grouped by main reason (reason from last study dose stopped). The percentages for the reasons will be calculated using the number of patients who discontinued the study treatment as denominator
- Number of patients who discontinued the 24-month study, grouped by main reason. The percentages for the reasons will be calculated using the number of patients who discontinued the study as denominator

10.2 Protocol Deviations

The analysis of the protocol deviations will be performed on the FAS, unless otherwise stated. Protocol deviations will be collected in a deviation log.

10.2.1 Important Protocol Deviations

The following summary table of important protocol deviations will be provided:

- Frequency table per reason of important protocol deviations

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

For Patients excluded from the PP, the reasons for exclusion will be summarized and listed;

- Frequency table per reason of exclusion from the PP population
- Listing of reasons of exclusion from the PP population (The listing will include patient ID and the Reason for exclusion from PP Analysis Set)

11 Demographics and Other Baseline Characteristics

If not stated otherwise, summaries will be presented on the FAS and PP populations. Missing values for the Baseline characteristics will be treated as described in section 9, unless otherwise stated.

11.1 Demographics

Demographic characteristics will be summarized using the following information from the Demographics eCRF pages.

- Demographic characteristics
  - Gender: male, female
  - Race: white, black or African American, Asian, Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, other
  - Ethnicity: Hispanic or Latino, Not Hispanic or Latino, Not reported, Unknown
  - Age (years)
  - Age categories:
    - <65 years,
    - ≥65 years:
      - 65-74, 75-84, ≥85
  - Weight.

Specifications for computation:

- Age [years]
  - (date of informed consent - date of birth + 1) / 365.25

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using Medical Dictionary for Regulatory Activities (MedDRA), current version, preferred term (PT) as event category and system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

It is recommended to use the most current MedDRA version at the time of data cutoff.

11.3 Other Baseline Characteristics

Summary statistics will be presented for:

- Elapsed time since diagnosis of MS (years)

- Proportion of patients with MS diagnosis <24 months (≥24 months) before study
- Elapsed time since first symptoms of MS (years)
- Baseline PRO data
- Baseline laboratory data
- Baseline data on previous MS DMD use
- Relapses during the previous 2 years (1 year, if MS diagnosis is <24 months)
- ARR (retrospective data)
- Baseline MRI data
- MRI data in the 2 years prior to study enrolment or since MS diagnosis, if diagnosis <24 months
- Past treatment adherence (collected via ePRO: MS-TAQ modified Self-Injectables Version to assess adherence during last previous injectable DMD treatment)
- Pregnancy and comorbid conditions (Human Immunodeficiency Virus [HIV], hepatitis B, hepatitis C, tuberculosis and JCV status).

Elapsed time since diagnosis of MS

The elapsed time since diagnosis of MS will be calculated as:

elapsed time since diagnosis of MS (days) = Informed consent date - Initial MS diagnosis date

elapsed time since diagnosis of MS (months) = (Informed consent date - Initial MS diagnosis date)/ 30.4375

elapsed time since diagnosis of MS (years) = (Informed consent date - Initial MS diagnosis date)/ 365.25

It will be summarized descriptively as a continuous variable.

Elapsed time since first symptoms of MS

The elapsed time since first symptoms of MS will be calculated as:

elapsed time since first symptoms of MS (days) = Informed consent date - First attack date

elapsed time since first symptoms of MS (months) = (Informed consent date - First attack date)/30.4375

elapsed time since first symptoms of MS (years) = (Informed consent date - First attack date)/365.25

It will be summarized descriptively as a continuous variable.

Relapses during the previous 2 years

The number of relapses during the previous 2 years (or since MS diagnosis if <2 years) and the duration of these relapses will be summarized descriptively as continuous variables.

ARR (retrospective data)

The ARR based on the last 24 months prior to the start of treatment with cladribine tablets will be assessed. The retrospective 24 months ARR for a patient is calculated as

*(No. of relapses within 24 months prior to written informed consent for that patient / (30.4375*24)) * 365.25*

For patients who were diagnosed with MS at least 12 months but less than 24 months prior to written informed consent, the number of relapses since MS diagnosis will be used and the ARR calculation will be:

*(No. of relapses since MS diagnosis and prior to written informed consent for that patient / (Informed consent date - Initial MS diagnosis date)) * 365.25*

Such a variable will be summarized descriptively.

Baseline PROs, laboratory and MRI data.

Baseline PROs, laboratory, and MRI data is anticipated to be collected before the first dose of cladribine tablets is taken.

Baseline PROs and laboratory data will be summarized descriptively as continuous variables.

Most recent MRI prior to starting cladribine tablets (baseline MRI), which is expected to have been taken within the prior 90 days, will be summarized descriptively considering the following continuous variables:

- number of T1 Gd+ lesions;
- number of new T2 lesions compared to most recent prior MRI;
- number of newly enlarging T2 lesions compared to most recent prior MRI;
- number of Combined Unique (CU) lesions;

and the following qualitative variables:

- presence of brain atrophy;
- presence of segmental atrophy.

Results of MRI in the 2 years prior to study enrolment will be summarized descriptively with respect to the above continuous variables for the lesions. The number and percentage of patients with brain atrophy or segmental atrophy in the previous 2 years will be reported. For patients who

were diagnosed with MS less than 24 months prior to written informed consent, MRI results since diagnosis will be summarized.

Baseline data on previous MS DMD use and past treatment adherence

DMD treatments received in the 2 years prior to study enrolment (including medication doses and routes of administration, start dates, stop dates, and reasons for discontinuation) will be collected. A listing with the above characteristics and the date of diagnosis will be presented.

For each previous DMD received for MS during the last 2 years the corresponding number and percentage of patients that received it will be presented. The corresponding reasons (number and percentage) for discontinuation will also be reported.

The number of previous DMD received for MS (a) during the last 2 years and (b) in total will be summarized descriptively considering them as continuous variables.

For patients who were diagnosed with MS at least 12 months but less than 24 months prior to written informed consent, DMD treatments received since diagnosis will be summarized.

Past treatment adherence data will be collected before the first dose of cladribine tablets is taken. Data collected at Baseline through the modified Self-Injectables Version of the MS-TAQ to assess adherence during last previous injectable DMD treatment will be summarized descriptively to assess adherence during last previous injectable DMD treatment.

Pregnancy and comorbid conditions

The number and percentages of patients with positive result will be reported for the following tests, if performed at baseline: Pregnancy, HIV, hepatitis B, hepatitis C, tuberculosis and JCV tests.

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13 Study Dose Compliance and Exposure

All dosing calculations and summaries will be based on the "Exposure" eCRFs pages.

The FAS (i.e., Safety) population will be used for the related summaries.

The number of planned 10 mg tablets will be determined as follows (where weight is in kg and refers to the baseline weight).

For patients in the initial treatment course in Year 1, for each treatment week:

1. *If weight <110 then 'Number of planned tablets' = nearest integer to (weight – 5)/10*
2. *If weight >= 110 then 'Number of planned tablets' = 10*

For patients in the second treatment course in Year 2, for each treatment week:

1. *If weight <80 then 'Number of planned tablets' = nearest integer to (weight – 5)/10*
2. *If weight ≥80 and weight <110 then 'Number of planned tablets' = nearest integer to (weight – 15)/10*
3. *If weight >= 110 then 'Number of planned tablets' = 10*

The planned dose (mg) is given by *'Number of planned tablets'*10.*

The planned dose (mg/kg) is given by *'planned dose (mg)'/weight.*

For each treatment week the actual number of tablets received is given by the 'Number of tablets' as recorded through the eCRF forms.

The actual dose (mg) is given by '*actual number of tablets'*10.*

The actual dose (mg/kg) is given by '*actual dose (mg)' /weight.*

Treatment adherence is one of the secondary endpoints and will be assessed through a questionnaire. It will be described in section 16.4.

Data on cladribine tablets treatment during the study period will be collected, including medication start dates, medication stop dates, medication dose (mg), number of doses and reasons for discontinuation, if applicable. A listing with at least the following characteristics will be presented:

- Patient ID
- Cladribine tablets Start Date
- Cladribine tablets Stop Date
- Visit
- Planned number of tablets
- Actual number of tablets
- Planned dose (mg/kg)
- Actual dose (mg/kg)
- Treatment compliance (%)
- Reason for dose adjustment
- Reason for no dose

The number of planned tablets, the planned dose (mg/kg) and the actual dose (mg/kg) will be provided. Treatment Compliance (%) is defined as Total actual number of Cladribine tablets / Total planned number of Cladribine tablets.

The number and percentage of patients who discontinue cladribine tablets will be reported.

The number and percentage of patients who started another MS treatment after discontinuation of cladribine tablets will be reported (using the number of patients who discontinue cladribine tablets as denominator).

Reasons for discontinuation of cladribine tablets will be collected and for each reason, the corresponding number and percentage of patients will be reported (using the number of patients who discontinue cladribine tablets as denominator).

A listing of concomitant MS medications started after discontinuation of cladribine tablets will be provided. The following variables will be reported:

- Patient ID
- Medication name
- Visit
- Dose
- Unit
- Frequency
- Route of administration
- Start Date / Ongoing (Yes/No) / Stop Date
- Last study treatment administration date

The elapsed time to discontinuation of cladribine tablets will be calculated as:

elapsed time to discontinuation of cladribine tablets = Date of discontinuation of cladribine tablets – Date of first study dose

It will be summarized as a continuous variable and also reported through a KM analysis. The 'Last study treatment administration date' according to the Treatment Termination form will be used as date of discontinuation of cladribine tablets (both for patients early discontinuing the treatment and for patients completing the treatment; for patients completing the treatment this will be a censoring date).

Number of doses and % of planned doses (as per USPI) received will be summarized descriptively.

14 Efficacy Analyses

14.1 Primary Endpoint: ARR

14.1.1 Primary Objective: Analysis of the ARR

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: ARR over 24 Months			
Primary (FAS) Secondary (PP)	*ARR over 24 Months.* *The ARR over 24 Months of a patient is calculated as the number of relapses of the patient divided by the number of days on study for that patient and multiplied by 365.25. This variable will be considered to get population estimates.* *A relapse will be defined as per routine clinical practice as determined by the investigator* *Time on Study (days) = (Date of Study Completion or Date of study discontinuation - Date of first dose of cladribine tablets +1)*	The population estimate will be based on the average of the ARR values for the patients in the study. The corresponding 95% CI will be reported. The Statistical Analysis Software (SAS)® MEANS procedure will be used to compute these quantities. The following descriptive statistics will be reported: mean, SD, min, max, median, first quartile (Q1) and third quartile (Q3).	Patients discontinuing early are analyzed according to number of years of follow-up on treatment and number of relapses observed at the time of discontinuation.
Sensitivity (FAS)	*Model based ARR, defined as expectation of relapses divided by time on study.*	The estimate of the expected ARR at Month 24 will be based on a Negative Binomial (NB) model for relapse count, with offset equal to the log of years on study and adjustment for categorical number of relapses in the last 2 years, or since MS diagnosis if diagnosis <24 months (≤1 relapse, >1 relapse). The NB regression will be computed with the SAS® GENMOD procedure, using the dist=NB option in the MODEL statement.	Same handling as for the primary analysis

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
		*The estimate of the expected ARR at Month 24 will be based on a Zero Inflated NB model for relapse count, with offset equal to the log of years on study and adjustment for categorical number of relapses in the last 2 years, or since MS diagnosis if diagnosis <24 months (≤1 relapse, >1 relapse). The NB regression will be computed with the SAS® GENMOD procedure, using the dist=ZINB option in the MODEL statement.	

ARR: Annualized Relapsed Rate; FAS: Full Analysis Set; GENMOD: Generalized Linear Model PP: Per Protocol; SAS: Statistical Analysis System.

* The sensitivity analysis with the zero inflated binomial model will be considered only if the number of patients without relapses is greater than 5%.

The primary endpoint is derived from the number of relapses collected through the eCRF forms "MS Relapse Report" and "MS Relapse Report Details". A patient will have 0 relapses (at Visit 3 and /or Visit 6) if replied "No" to the leading question "Has patient experienced a new MS relapse since last scheduled or unscheduled visit? (Yes, No)". For patient replying 'Yes', the number of relapses will be derived from the records in the "MS Relapse Report Details" form. If at Visit 3 the answer to the leading question is not collected, then the number of relapses in the first year and the total number of relapses during the second year will be missing. If at Visit 6 the answer to the leading question is not collected, then the number of relapses during the second year will be missing.

For ongoing patients during the study, the Time on Study will take into account the last available date of a patient. This will be used in the interim analyses for all ARR evaluations (primary objective, sensitivity analyses and secondary analyses).

14.1.2 Sensitivity Analyses of the ARR

For the NB model the Least Squares means estimates of the ARR at Month 24 and associated CI will be reported for patients having respectively ≤1 relapse or >1 relapse in the previous 2 years, or since MS diagnosis if diagnosis <24 months. These quantities will be obtained using the LSMEANS statement with the ILINK option.

For the Zero Inflated NB model, the following approach will be used to report the estimates of the ARR at Month 24 and associated CIs for patients having respectively ≤1 relapse or >1 relapse in the previous 2 years, or since MS diagnosis if diagnosis <24 months. The STORE statement in PROC GENMOD will be used to save the fitted model. Then the fitted model will be used in proc PLM with the SCORE statement and the ILINK and NOOFFSET option.

Standardized deviance residuals will be plotted against the linear predictor to assess the goodness of fit of the model (NB or Zero inflated NB). The STDRESDEV statement with the XBETA option in the GENMOD procedure will be used.

14.1.3 Secondary Analyses of the ARR

The secondary analysis of the primary endpoint (ARR at Month 24) will be conducted on the PP population using the same method of the primary analysis.

14.1.4 Subgroup Analyses of ARR

The subgroup analyses of the primary endpoint (at Month 24 for the ARR during the follow-up period) will be conducted on the FAS population.

A subgroup analysis at Month 24 of the ARR during the follow-up period for patients completing the study and patients who drop out will be performed. Estimates and CIs for the 2 subgroups will be reported using the same method of the primary analysis.

The same analysis will be performed for patients completing the treatment and patients who do not complete the treatment (i.e., completing Year 1 treatment but not Year 2 treatment) when the number of patients in the last group is greater than 10.

A subgroup analysis at Month 24 of the ARR during the follow-up period will be performed with reference to the type of MS at screening (RRMS, aSPMS, PPMS and CIS).

For the primary outcome, the patterns of missingness will be explored. When the number of missing values is substantial (>5%), multiple imputation methodology will be considered for the analysis of the primary objective. At least 20 imputed datasets will be considered. The ARR at Month 24 for a patient will be considered missing if for that patient the number of relapses at Month 24 is missing or if the Time on Study for that patient is missing. At least the following variables will be considered in the imputation model:

- ARR at Month 24
- Type of MS at screening
- Number of relapses in the previous 2 years
- Age
- Sex
- Baseline Body Mass Index (BMI)
- Compliance

Since we have both continuous and categorical variables in the imputation model the Fully Conditional Specification method will be considered for the imputation. Predictive mean matching will be used for the imputation of the following variables: ARR at Month 24, number of relapses in the previous 2 years, age, baseline BMI and compliance. SAS code for the analysis is available in the appendices.

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15 Safety Analyses

Safety analyses will be done on the safety analysis populations, i.e. SAF for the first 24-month period.

15.1 Adverse Events

Definitions

The recording period for AEs begins when the patient is initially included in the study (date of signature of first informed consent) and continues at least to the end of the mandatory safety follow-up period (i.e., up to 24 months in most patients or up to 30 months in patients with delayed start of Year 2 treatment).

TEAEs: those AEs with onset dates occurring within the treatment period (that is after the first dose and until the end of the follow-up period).

For the analyses, ADRs will be those TEAEs reported in the eCRFs as related to study treatment or those AEs where such a relationship is missing.

All analyses described in Section 15.1 will be based on TEAEs if not otherwise specified.

Event rates (per patient-year of time on the study) will be calculated as the total number of events divided by the total time on study.

Missing data handling

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study dose then the onset date will be replaced by the minimum of the start of study dose and AE resolution date.
- In all other cases, the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of patient's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed. If Stop date of AE is after the date of cutoff outcome of AE is ongoing at cutoff.

15.1.1 All Adverse Events

If an AE is reported for a given patient more than once during the study, the worst severity and the worst relationship to study drug will be tabulated.

The following overall frequency table will be prepared:

- Any TEAEs
- Treatment related TEAEs (ADRs)
- Any serious TEAEs
- Treatment related serious TEAEs
- Any TEAE by severity (Severe, Moderate, Mild)
- Treatment related TEAE by severity (Severe, Moderate, Mild)
- TEAEs leading to death
- Treatment related TEAEs leading to death.

The total number of TEAEs and rate (per patient-year of time on study) of TEAEs will be also reported.

A table showing the TEAE by Primary SOC and PT will be reported.

A listing with the following columns will be presented:

- Patient ID
- AE

- PT term
- Start/ End Date of AE
- Duration of AE (days)
- Relationship to Cladribine
- Action on Cladribine
- Outcome
- Relative Day from First Administration
- SAE (Yes/No).

15.1.2 Adverse Events Leading to Study Treatment Discontinuation

The following overall frequency table will be prepared:

- TEAEs causing temporary discontinuation of study treatment
- TEAEs causing permanent discontinuation of study treatment
- Any TEAE leading to dose reduction of study treatment.

For the above categories the total number and rate (per patient-year of time on study) of TEAEs will be also reported.

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

15.2.1 Deaths

The following summaries for the deaths will be reported in a table:

- Number and percentage of Deaths
- Number and percentage for each Reason of Death (percentage calculated using the number of deaths as denominator).

The total number of deaths and rate (per patient-year of time on study) of deaths will be also reported.

A listing with the following columns will be presented:

- Patient ID
- Age (years)/ Sex/ Race/ Weight (kg)
- Date of first / last administration
- Last dose (unit)
- Number of doses

- Date of death
- Cause of death
- AE
- PT term.

15.2.2 Serious Adverse Events

A listing with the following columns will be presented:

- Patient ID
- AE
- PT term
- Start/ End Date of AE
- Duration of AE (days)
- Seriousness criteria (Results in death, Is life-threatening, Requires/Prolongs Hospitalization, Persistent/Significant Disability/Incapacity, Is a Congenital Anomaly/Birth Defect, Other)
- Relationship with study treatment (Related, Unrelated)
- Severity (Severe, Moderate, Mild)
- Action(s) taken with study treatment
- Outcome of Event (Fatal, Not recovered/not resolved, Recovered/resolved with sequelae, Recovered/resolved, Unknown)
- Relative Day from First Administration.

15.3 Clinical Laboratory Evaluation

Hematology assessment will be based on white blood cell count, hemoglobin, hematocrit, platelet count, ALC. For continuous variables, values and change from baseline values will be considered. The above variables will be evaluated descriptively by time point.

Any available results from JCV tests done will be summarized as status positive or negative. It will be summarized descriptively at baseline and for all the tests available during the study a listing with

- Patient ID
- Date of JCV test
- JCV test done? (Done/Not Done)
- Result (Positive or Negative)

will be reported.

Any available results for immunoglobulin will be summarized as continuous variable, with values and change from baseline values by timepoint.

Laboratory values that are outside the normal range will also be flagged in the data listings, along with corresponding normal ranges. The data listing will include the following columns:

- Patient ID
- Parameter (International System of Units (SI unit))
- Visit/Week
- Date of Collection (Relative Day)
- Value
- Change from Baseline
- Lower Range/Upper Range
- Normal Range Indicator (Low, High).

Boxplots of the laboratory values and boxplots of the change from baseline values will be reported by time point.

ALC will also be displayed as a line graph with the median cell counts on the y-axis (with bars for 1st and 3rd quartile extending above and below) and time points on the x-axis.

An additional summary of ALC by lymphopenia grade will be presented with proportion of patients in each category at each time point:

- Elevated: >4.8 x 109 cells/L
- Normal: 1.0 to 4.8 x 109 cells/L
- Grade 1 Lymphopenia: 0.8 to <1.0 x 109 cells/L
- Grade 2 Lymphopenia: 0.5 to <0.8 x 109 cells/L
- Grade 3 Lymphopenia: 0.2 to <0.5 x 109 cells/L
- Grade 4 Lymphopenia: <0.2 x 109 cells/L

These categories are consistent with the Common Terminology Criteria for Adverse Event (CTCAE) for lymphopenia AE grading (US Department of Health and Human Services. CTCAE version 4.0. 2009;4(03)).

15.4 Vital Signs

Weight will be collected at Baseline when available. It will be summarized descriptively.

Unit Conversion:

Weight (Kg) = 0.4536* Weight (lb)

15.5 Other Safety or Tolerability Evaluations

Physical examination as per standard of care will be performed at Baseline. The number and percentage of patients completing the physical examination will be reported.

Neurological examination as per standard of care will be performed at Baseline and at Visit 2, 3, 5 and 6. During the examination, if Kurtzke Functional System Scores , ambulation up to 500 meters and Expanded Disability Status Score are collected as standard of care, they will be reported and evaluated. No imputation will be performed if any items in the above examinations are missing. Visit values (including Baseline) and change from baseline values will be considered. All the items will be summarized descriptively.

16 Analyses of Other Endpoints

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16.3 Patient-Reported Outcome

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary Endpoints: ePROs			
Secondary (FAS)	*Scores collected at Baseline and at Month 6, 12 and 24 for the following PROs (TSQM, SF-36, MFIS-5, BDI-FS, WPAI-MS)*	Baseline scores and change from baseline scores will be summarized descriptively	See description in section 16.3
	Scores collected at Baseline and at Month 6, 12, and 24 for PDDS	Baseline scores and change from baseline scores will be summarized descriptively	See description in section 16.3

BDI-FS: Beck-Depression Inventory-Fast Screen; FAS: Full Analysis Set; MFIS-5: Modified Fatigue Impact Scale – 5-Item Version; MS: Multiple Sclerosis; PDDS: Patient Determined Disease Steps; SF-36: 36-Item Short Form Health Survey; TSQM: Treatment Satisfaction Questionnaire for Medication, WPAI-MS: Work Productivity Activity Impairment.

TSQM

TSQM-14 is an instrument to assess patient's satisfaction with medication, providing scores on 4 scales: side effects, effectiveness, convenience and global satisfaction. With the exception of item (i.e., question) 4 (presence of side effects; yes or no), all items have 5 or 7 responses, scored

from 1 (least satisfied) to 5 or 7 (most satisfied). Higher scores indicate higher 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.

Global Satisfaction
([(Sum (Item 12 to Item 14)) – 3] divided by 14) * 100
If Item 12 or 13 is missing:
([(Sum (the 2 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 2 completed items)) – 2] divided by 12) * 100

Side Effects
If Question 4 is answered 'No' then score = 100
Else
([Sum (Item 5 to Item 8) – 4] divided by 16) * 100
If one item is missing:
([(Sum (the 3 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 2 completed items)) – 2] divided by 12) * 100

The 14 items are listed in the Appendices.

Each derived score will be summarized descriptively as a continuous variable.

SF-36

SF-36 is a self-administered, generic health status questionnaire consisting of 36 questions that measure 8 health concepts: physical functioning, role limitations due to physical problems, bodily pain, general health perception, vitality, social functioning, role limitations due to emotional problems and mental health (MH).

The SF-36 has a single item covering change in health status over the last year and 8 multi-item scales. Two summary scales (Physical and Mental) have also been derived using factor analytic methods. Scales are set up so that a higher score indicates better health.

The SF-36 questionnaire is reported in the Appendices.

The reference tool for the derivation of the composite scores will be the scoring software provided by Optum, PRO CoRE: SF-36v2.

The algorithm used by this software has 5 steps for the scoring of the profile scales:

1. Data Cleaning and Item Recoding
2. Item Recalibration
3. Computation of Raw Scores
4. Transformation of Raw Scale Scores to 0-100 Scores
5. Transformation of 0-100 Scores to T-score Based Scores

After these steps, the component summary measures are derived as follows:

1. Standardization of the SF-36v2® Health Survey Scales
2. Aggregation of the Scale Scores
3. Transformation of Summary Scores

Details for the above steps are included in the manual provided with the software.

Missing item can be replaced using Maximum Data Recovery (Max). With this method the software applies a value to a scale item rendered missing if at least one of the items in that scale has valid data. A scale receives a "missing" score (".") only if all the items in that scale are missing. Physical Components Summary Score (PCS) and Mental Component Summary Score (MCS) are calculated when at least 7 of the 8 profile scales have valid data, either actual or estimated.

However, to calculate PCS, the Physical Function (PF) scale must be one of the 7 scales having valid data. Also, to calculate MCS, the MH scale must be one of the 7 scales having valid data.

MFIS-5

MFIS-5 is a modified form of the Fatigue Impact Scale that consists of 5 questions that assess the impact of fatigue on physical, cognitive, and psychosocial functioning, with 5 response levels ranging from 0 ("Never") to 4 ("Almost always"). Total scores range from 0 to 20, with higher scores representing a greater impact of fatigue.

Consider the following scale: 0 (Never), 1 (Rarely), 2 (Sometimes), 3 (Often), 4 (Almost always).

The following items from the MFIS constitute the MFIS-5:

- I have been less alert
- I have been limited in my ability to do things away from home
- I have had trouble maintaining the physical effort for long periods
- I have been less able to complete tasks that require physical effort
- I have had trouble concentrating.

Each item (and the total score) will be summarized descriptively considering the raw scores as values of a continuous variable.

No imputation will be performed if any items in the MFIS-5 are missing.

BDI-FS

The 7 items BDI-FS is a self-report inventory for measuring the severity of depression on a 7-item scale. The BDI-Fast Screen is scored by summing all of the highest ratings for each of the 7 items. Each item is rated on a 4-point scale ranging from 0 to 3. The maximum total score is 21. Higher scores indicate greater symptom severity. If an examine has multiple endorsements for an item, then the statement with the highest rating should be scored.

The 7 items are the following: Sadness, Pessimism, Past Failure, Loss of Pleasure, Self-Dislike, Self-Criticalness, Suicidal Thoughts.

Each item (and the total score) will be summarized descriptively considering the raw scores as values of a continuous variable.

No imputation will be performed if any items in the BDI-FS are missing.

WPAI-MS

The WPAI-MS questionnaire is a 6-items validated instrument to measure impairments in work and activities. The WPAI yields 4 types of scores: 1. Absenteeism (work time missed); 2. Presenteeism (impairment at work/reduced on-the-job effectiveness); 3. Work productivity loss (overall work impairment/absenteeism plus presenteeism); 4. Activity Impairment. WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity.

WPAI outcomes are expressed as impairment percentages, with higher numbers indicating greater impairment and less productivity, i.e., worse outcomes, as follows:

Questions:

1 = Are you currently employed (working for pay)?

2 = During the past 7 days, how many hours did you miss from work because of problems associated with your multiple sclerosis (MS)?

3 = During the past 7 days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

4 = During the past 7 days, how many hours did you actually work?

5 = During the past 7 days, how much did your MS affect your productivity while you were working? (Scale 0-10)

6 = During the past 7 days, how much did your MS affect your ability to do your regular daily activities, other than work at a job? (Scale 0-10)

Scores:

Multiply scores by 100 to express in percentages.

1. Percent work time missed due to health: Q2/(Q2+Q4)
2. Percent impairment while working due to health: Q5/10

3. Percent overall work impairment due to health: Q2/(Q2+Q4)+[(1-(Q2/(Q2+Q4)))x(Q5/10)]
4. Percent activity impairment due to health: Q6/10

Each score (percentage) will be summarized descriptively as a continuous variable.

No imputation will be performed if any items in the WPAI-MS are missing.

PDDS

The PDDS is a patient-reported scale to assess the disability status in patients with MS and it focuses mainly on how patients walk. A higher score represents a higher level of disability. Scores on the PDDS range from 0 (normal) to 8 (bedridden): 0 (Normal), 1 (Mild Disability), 2 (Moderate Disability), 3 (Gait Disability), 4 (Early Cane), 5 (Late Cane), 6 (Bilateral Support), 7 (Wheelchair/Scooter) and 8 (Bedridden).

This single item will be summarized descriptively as a continuous variable using the raw scores.

No imputation will be performed if any values in the PDDS are missing.

16.4 Treatment Adherence

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
secondary Endpoint: Treatment adherence			
Secondary (FAS)	*Treatment adherence based on modified versions of the MS-TAQ. Data collected at baseline and at Months 1, 2, 13 and 14*	Baseline scores over time will be summarized descriptively	See description in Section 16.4

FAS: Full Analysis Set; MS-TAQ: Multiple Sclerosis Treatment Adherence Questionnaire

Treatment adherence questions

Seven treatment adherence questions, based on modified versions of the MS-TAQ, were developed to determine level of adherence as well as identify barriers to adherence for MS patients taking DMDs. A Self-Injectables Version of the MS-TAQ has been proposed to assess adherence to last previous injectable DMD treatment at Baseline. Another version of the MS-TAQ has been modified for cladribine tablets to assess adherence to cladribine tablets throughout the study.

For both versions the single questions will be summarized descriptively. Items on an ordinal scale will be summarized as continuous variables. No imputation will be performed if any values in the MS-TAQ are missing.

The modified versions of the MS-TAQ are reported in the Appendices.

17 References

No references.

18 Appendices

TSQM items

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

(Score 1 to 7)

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

(Score 1 to 7)

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

(Score 1 to 7)

4. As a result of taking this medication, do you currently experience any side effects at all?

(Score 0[No] or 1[Yes])

5. How bothersome are the side effects of the medication you take to treat your condition?

(Score 1 to 5)

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy level, etc.)?

(Score 1 to 5)

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

(Score 1 to 5)

8. To what degree have medication side effects affected your overall satisfaction with the medication?

(Score 1 to 5)

9. How easy of difficult is it to use the medication in its current form?

(Score 1 to 7)

10. How easy or difficult is it to plan when you will use the medication each time?

(Score 1 to 7)

11. How convenient or inconvenient is it to take the medication as instructed?

(Score 1 to 7)

12. Overall, how confident are you that taking this medication is a good thing for you?

(Score 1 to 5)

13. How certain are you that the good things about your medication outweigh the bad things? (Score 1 to 5)

14. Taking all things into account, how satisfied or dissatisfied are you with this medication? (Score 1 to 7)

HEALTH STATUS QUESTIONNAIRE (SF-36)

This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please select the one response that best describes your answer.

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
	• Your Health and Well-Being						
	• This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey! For each of the following questions, please select the one response that best describes your answer.						
SF36v2_GH1	In general, would you say your health is:	Excellent	Very good	Good	Fair	Poor	
SF36v2_HT	Compared to one year ago, how would you rate your health in general now?	Much better now than one year ago	Somewhat better now than one year ago	About the same as one year ago	Somewhat worse now than one year ago	Much worse now than one year ago	
	The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?						
SF36v2_PF01	Does your health now limit you in vigorous activities, such as running, lifting heavy objects, participating in strenuous sports? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF02	Does your health now limit you in moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF03	Does your health now limit you in lifting or carrying groceries? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF04	Does your health now limit you in climbing several flights of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF05	Does your health now limit you in climbing one flight of stairs? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF06	Does your health now limit you in bending, kneeling, or stooping? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF07	Does your health now limit you in walking more than a mile? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF08	Does your health now limit you in walking several hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF09	Does your health now limit you in walking one hundred yards? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			
SF36v2_PF10	Does your health now limit you in bathing or dressing yourself? If so, how much?	Yes, limited a lot	Yes, limited a little	No, not limited at all			

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of your physical health?						
SF36v2_RP1	During the past 4 weeks, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP2	During the past 4 weeks, how much of the time have you accomplished less than you would like as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP3	During the past 4 weeks, how much of the time were you limited in the kind of work or other activities as a result of your physical health?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RP4	During the past 4 weeks, how much of the time have you had difficulty performing the work or other activities as a result of your physical health (for example, it took extra effort)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
	During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?						
SF36v2_RE1	During the past 4 weeks, how much of the time have you cut down on the amount of time you spent on work or other activities as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RE2	During the past 4 weeks, how much of the time have you accomplished less than you would like as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_RE3	During the past 4 weeks, how much of the time have you done work or other activities less carefully than usual as a result of any emotional problems (such as feeling depressed or anxious)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_SF1	During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	Not at all	Slightly	Moderately	Quite a bit	Extremely	
SF36v2_BP1	How much bodily pain have you had during the past 4 weeks?	None	Very mild	Mild	Moderate	Severe	Very severe
SF36v2_BP2	During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	Not at all	A little bit	Moderately	Quite a bit	Extremely	
	These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling.						

Item Name	Question Text	Answer Text 1	Answer Text 2	Answer Text 3	Answer Text 4	Answer Text 5	Answer Text 6
SF36v2_VT1	How much of the time during the past 4 weeks did you feel full of life?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH1	How much of the time during the past 4 weeks have you been very nervous?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH2	How much of the time during the past 4 weeks have you felt so down in the dumps that nothing could cheer you up?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH3	How much of the time during the past 4 weeks have you felt calm and peaceful?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT2	How much of the time during the past 4 weeks did you have a lot of energy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH4	How much of the time during the past 4 weeks have you felt downhearted and depressed?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT3	How much of the time during the past 4 weeks did you feel worn out?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_MH5	How much of the time during the past 4 weeks have you been happy?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_VT4	How much of the time during the past 4 weeks did you feel tired?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
SF36v2_SF2	During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?	All of the time	Most of the time	Some of the time	A little of the time	None of the time	
	How TRUE or FALSE is each of the following statements for you?						
SF36v2_GH2	I seem to get sick a little easier than other people.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH3	I am as healthy as anybody I know.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH4	I expect my health to get worse.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
SF36v2_GH5	My health is excellent.	Definitely true	Mostly true	Don't know	Mostly false	Definitely false	
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MS-TAQ Modified Self-Injectables Version to assess adherence during last previous injectable DMD treatment

1.) Before enrolling in this study, what self-injectable medication were you taking to treat your Multiple Sclerosis (MS)? (Check one)

Avonex (interferon beta 1a --- intramuscular)	
Betaseron (interferon beta 1b --- subcutaneous)	
Copaxone (glatiramer acetate)	
Extavia (interferon beta 1b)	
Glatopa (glatiramer acetate)	
Plegridy (peginterferon beta 1a)	
Rebif (interferon beta 1a --- subcutaneous)	
Other, please specify:	

2.) During the last 4 weeks (28 days) that you were taking this medication, how many days were you supposed to take this medication? (Check one)

Every day (28 times)	
Every other day (14 times)	
Three times a week (12 times)	
Once a week (4 times)	
Once every two weeks (2 times)	
Other, please specify:	

3.) Did you miss or forget to take any doses of this medication during the last 4 weeks (28 days) that you were taking the medication? (Check one)

Yes	
No	

4.) How many doses did you miss or forget to take? (Complete blank)

IF YOU HAVEN'T SKIPPED ANY DOSES IN THE PAST 28 DAYS, SKIP TO QUESTION 6

(Complete this section only if you missed a dose in the past 28 days)

5.) How important were the following factors in missing or forgetting to take a dose? (Please check one answer for each)

	Not important at all	A little important	Moderately important	Extremely important
Memory problems	0	1	2	3
Too busy	0	1	2	3
Side effects of injection	0	1	2	3
Fear of needles	0	1	2	3
Needing someone to help me take my medication	0	1	2	3
Ran out of medication or could not refill my prescription	0	1	2	3
Away from home and could not access my medication	0	1	2	3
Feeling anxious, depressed, or nervous about taking my medication	0	1	2	3
Dissatisfaction with my medication	0	1	2	3
Did not want taking my medication to interfere with activities	0	1	2	3
Tired of taking my medication	0	1	2	3
Did not feel like taking my medication	0	1	2	3

6.) Overall, how hard or easy do you feel it is to take your most recent Multiple Sclerosis treatment as recommended by your physician? (Check one)

Extremely easy	1
A little hard	2
Moderately hard	3
Very hard	4
Extremely hard	5

7.) Overall, how satisfied are you with how things have been with your treatment during the past 4 weeks (28 days)? (Check one)

Not satisfied at all	1
A little satisfied	2
Moderately satisfied	3
Very satisfied	4
Completely satisfied	5

MS-TAQ modified for cladribine tablets

1.) What treatment week of cladribine tablets did you most recently complete? (check one)

Year 1, Treatment Week 1	
Year 1, Treatment Week 2	
Year 2, Treatment Week 1	
Year 2, Treatment Week 2	
Other, please specify:	

2.) How many cladribine tablets were you supposed to take during this treatment week? (complete the blank)

3.) Did you miss or forget to take any cladribine tablets during this treatment week? (Check one)

Yes	
No	

4.) How many cladribine tablets did you miss or forget to take? (Complete blank)

IF YOU HAVEN'T SKIPPED ANY DOSES IN THE PAST 28 DAYS, SKIP TO QUESTION 6

(Complete this section only if you missed a dose in the past 28 days)

5.) How important were the following factors in missing or forgetting to take a dose? (Please check one answer for each)

	Not important at all	A little important	Moderately important	Extremely important
Memory problems	0	1	2	3
Too busy	0	1	2	3
Side effects of medication	0	1	2	3
Ran out of medication or could not refill my prescription	0	1	2	3

	Not important at all	A little important	Moderately important	Extremely important
Away from home and could not access my medication	0	1	2	3
Feeling anxious, depressed, or nervous about taking my medication	0	1	2	3
Dissatisfaction with my medication	0	1	2	3
Did not want taking my medication to interfere with activities	0	1	2	3
Tired of taking my medication	0	1	2	3
Did not feel like taking my medication	0	1	2	3

6.) Overall, how hard or easy do you feel it is to take cladribine tablets as recommended by your physician during your treatment week? (Check one)

Extremely easy	1
A little hard	2
Moderately hard	3
Very hard	4
Extremely hard	5

7.) Overall, how satisfied are you with how things have been with your cladribine tablet treatment during your treatment week? (Check one)

Not satisfied at all	1
A little satisfied	2
Moderately satisfied	3
Very satisfied	4
Completely satisfied	5

SAS code for multiple imputation analysis (example)

The following SAS code is a reduced example that can be adapted for the analysis:

```
* aval is the ARR at month 24 ;
proc mi data=RELAPDATA out=ARRmiout nimpute=20 seed=123;
    class sex;
    fcs regpmm(blweight aval age);
    var age aval blweight sex;
run;

proc means data= ARRmiout N MEAN STD STDERR MIN MAX;
    by _Imputation_;
    var aval;
    output out=ARRmeans_imputed N=n MEAN=mean STD=std STDERR=stderr
MIN=min MAX=max;
run;

proc mianalyze data= ARRmeans_imputed;
    modeleffects mean;
    stderr stderr;
run;
```

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)	17 May 2024 06:36:57 UTC
PPD	Document Approval (I certify that I have the education, training and experience to perform this task)	20 May 2024 16:31:47 UTC