Title Page

CLOCK-MS Statistical Analysis Plan

Study Title	CLadribine Tablets: Collaborative Study to Evaluate the Impact On Central Nervous System BiomarKers in Multiple Sclerosis (CLOCK-MS)
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Version	1.1
Date	04 March 2024

CLOCK-MS
STATISTICAL ANALYSIS PLAN

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1 Administrative Information

Study Title: CLadribine Tablets: Collaborative Study to Evaluate the Impact On Central Nervous System BiomarKers in Multiple Sclerosis (CLOCK-MS)

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Related to Local Protocol #:	**EMD** MS700568_0049
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Biostatistician:	Amber Salter, PhD Associate Professor, Biostatistics The University of Texas Southwestern Medical Center Department of Neurology Section on Statistical Planning & Analysis 5323 Harry Hines Blvd. Dallas, TX 75390-8806

1.1 List of Revisions

Version: 1.0 **Date:** *16 November 2023*
Version: 1.1 **Date:** *04 March 2024*

1.2 SAP Signatures/Approvals

The undersigned have reviewed the format and content of this prospective statistical analysis plan (SAP) and have approved it for use to analyze the *CLOCK-MS* study data.

Name	Role	Affiliation	Signature	Date
Dr. Gregory Wu	Principal Investigator	Washington University St Louis	DocuSigned by: Gregory Wu, MD, PhD F2218E9D6C6A46F...	3/5/2024 | 9:11 AM CST
Dr. Amber Salter	Biostatistician	University of Texas Southwestern Medical Center	DocuSigned by: Amber Salter, PhD 5ABD448B420D430...	3/5/2024 | 9:12 AM CST
Ms. Samantha Lancia	Data Analyst	University of Texas Southwestern Medical Center	DocuSigned by: Samantha Lancia C30761B0362A495...	3/5/2024 | 9:59 AM CST

1.3 List of Abbreviations and Definitions of Terms

See Appendix 5 for a list of abbreviations defined within the CLOCK-MS protocol. Additional terms unique to this SAP are listed below:

1.4 Modification History

Unique Identifier for SAP version	Date of SAP version	Author	Changes from the Previous Version
1.0	16 November 2023	Samantha Lancia, MS & Amber Salter, PhD	N/A - original
1.1	04 March 2024	Amber Salter, PhD	Added z-scores for NfL

1.5 Purpose of the Statistical Analysis Plan

The purpose of this statistical analysis plan (SAP) is to document technical and detailed specifications for the analysis of data collected for protocol MS700568-0049. Results of the analyses described in this SAP will be included in Clinical Study Report (CSR). Any post-hoc or unplanned analyses performed to provide results for inclusion in the CSR but not identified in the prospective SAP will be clearly identified in the given CSR.

The SAP is prepared in compliance with the International Council on Harmonsation (ICH) E9.

2 Study Methods

2.1 Introduction

2.1.1 Background and Rationale

The purpose of this exploratory study is to better understand the mechanism of action (MoA) of cladribine tablets by exploring the effect on central nervous system (CNS) biomarkers relevant in the relapsing forms of multiple sclerosis (RMS; including relapsing-remitting MS [RRMS] and active secondary progressive MS). The study is designed to generate hypotheses regarding the impact and relevance of cladribine tablet activity in the CNS by assessing the cerebrospinal fluid (CSF) levels of lymphocyte subsets, other immune cells, neuronal injury markers, and soluble immunological markers in study participants with RMS before and during treatment with cladribine tablets, and the association of these CSF markers with corresponding blood markers and with clinical outcomes.

For cladribine specifically, a single study has shown that the proportion of MS patients with oligoclonal bands expression in the CSF decreases after treatment with parenteral cladribine (Rejdak, 2019). The effects of cladribine tablets on other cellular or soluble CSF biomarkers has not been evaluated to date.

In the CLOCK-MS study, the NfL levels in the CSF assessed before and at different time points during treatment with cladribine tablets will therefore be the primary soluble marker. Other soluble CSF and serum markers related to inflammation (e.g. CSF levels of immunoglobulin [Ig] G and IgM, and oligoclonal bands) and neurodegeneration (e.g. serum levels of neurofilament heavy chain [NfH]) will be assessed as exploratory markers. Up to now, the search for potential biomarkers in MS has been largely hypothesis-driven. Single soluble molecules or sets of molecules have been examined, based on their presumed association with key aspects of MS disease pathophysiology. More recent technologies such as RNA profiling allow for an unbiased screen to identify new candidate biomarkers. Such candidate biomarkers can then be further investigated with hypothesis-driven approaches to explore their role in the pathogenesis of MS and if they might be used as surrogate endpoints for treatment efficacy. Therefore, this study also includes the option for single cell RNA profiling and for RNA sample banking.

Additional background information and rationale for the analyses may be found in the study protocol.

2.1.2 Objectives

The interim analysis will evaluate the following objectives and endpoints:

Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)
Primary	
• To evaluate changes in the CSF levels of lymphocyte subtypes (CD3+ T lymphocytes, CD19+ B lymphocytes) and markers of neuronal injury (NfL) during treatment with cladribine tablets in patients with RMS	• Change in CSF levels of CD3+ T lymphocytes, CD19+ B lymphocytes, and NfL from baseline to second LP (end of Week 5, end of Week 10, or end of Year 1, and/or end of Year 2[a])

Objectives	Endpoints (Outcome Measures)
Secondary	
• To evaluate changes in the CSF levels of other lymphocyte subtypes and immune cells during treatment with cladribine tablets	• Change in CSF levels of CD4+ and CD8+ cells, plasmablasts, NK cells, Tregs, and CD14+ cells from baseline to second LP (end of Week 5, end of Week 10, or end of Year 1, and/or end of Year 2[a])
• To assess cladribine CSF and serum levels during treatment with cladribine tablets	• Cladribine CSF and serum concentrations at baseline and second LP (end of Week 5 time point only)
• To assess the peripheral blood levels of lymphocyte subtypes, other immune cells, and soluble immunological and neuronal injury markers during treatment with cladribine tablets.	• Change in peripheral blood levels of CD3+, CD4+ CD8+, CD19+, Th1, Th2, and Th17 cells, Tregs, plasmablasts, NK cells, CD14+ cells, and NfL levels from baseline to second LP (end of Week 5, end of Week 10, or end of Year 1, and/or end of Year 2[a])
• To collect safety data (adverse events, hematology) during treatment with cladribine tablets.	• Occurrence of TEAEs, SAEs, and TEAEs leading to treatment discontinuation • Absolute lymphocyte count assessed per USPI • Complete blood cell count as assessed per routine clinical practice

2.2 Methods

2.2.1 Study Design

This is an open-label, randomized, multicenter collaborative research Phase 4 biomarker study, designed to generate hypotheses to better understand the MoA of cladribine tablets in RMS. Approximately 50 study participants with RMS who met all eligibility criteria, and who were willing and able to receive lumbar punctures (LPs), were planned to be enrolled at 5 centers in the United States. Participants were required to be naïve to treatment with cladribine tablets.

The total duration of this interventional study will be 2 years for each participant. Approximately 50 study participants with RMS who meet the criteria for treatment with cladribine tablets per the approved USPI, and who are willing and able to receive LPs, are planned to be enrolled and randomized at 5 centers in the US. All study participants will receive treatment with cladribine 10 mg tablets during Year 1 and Year 2 according to the approved USPI (EMD Serono, 2019). Cladribine 10 mg tablets will be provided as commercial material.

Blood sampling will be aligned with the timing of the LPs (see **Error! Reference source not found.** and SoA in Section 1.3 of the study protocol). All study participants will have LP-aligned blood samples taken at baseline (on the same day as the baseline LP), and post-baseline at Week 5, end of Week 10, Year 1, and Year 2). If an LP is scheduled, the LP-aligned blood sampling will be done on the same day.

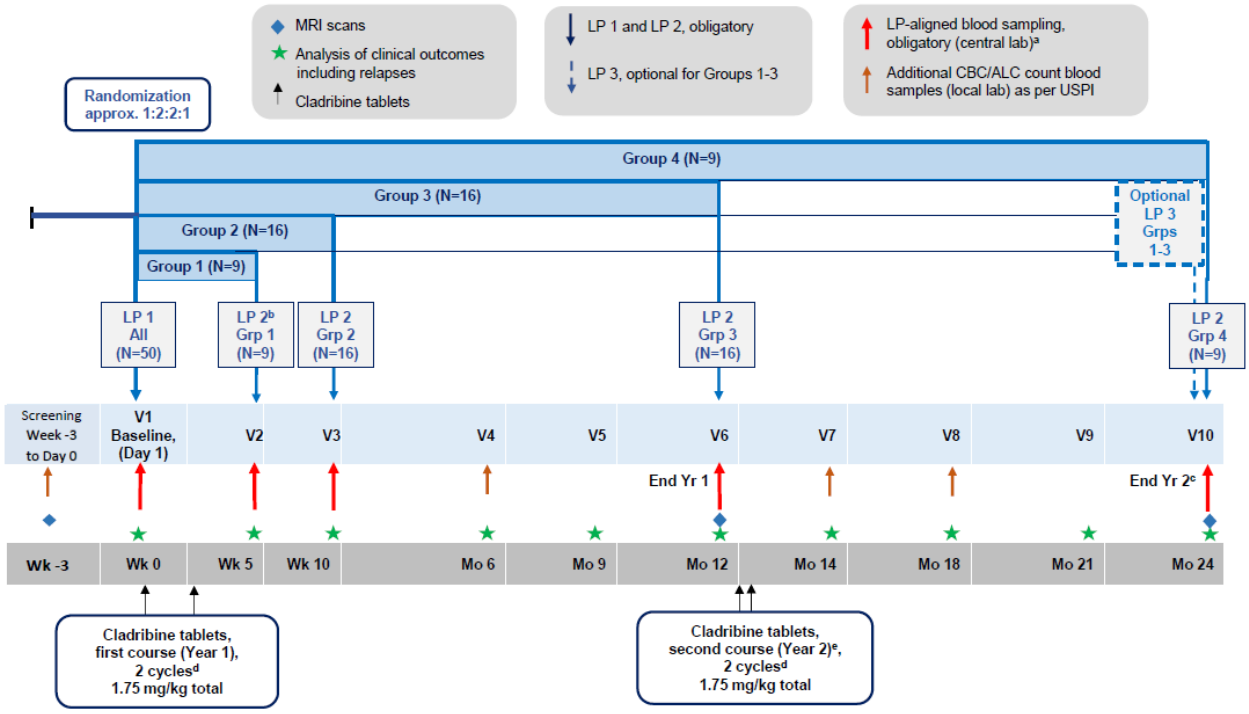

Figure 1. Study Schema.

Samples of the CSF- and the LP-aligned total blood samples will be sent to the central laboratory for cladribine concentration measurement (Section **Error! Reference source not found.** of the study protocol) and for soluble biomarker assessments (Section **Error! Reference source not found.** of the study protocol); cellular biomarkers will be assessed locally (Section **Error! Reference source not found.** of the study protocol). All cellular markers and NfL levels will be assessed in both CSF and peripheral blood. Other soluble biomarkers will be assessed in CSF or serum only, as appropriate (Section **Error! Reference source not found.** of the study protocol).

In addition, physicians are expected to monitor participants' ALC in accordance with the cladribine tablets USPI and to follow any other recommended monitoring and guidance as specified in the USPI (EMD Serono, 2019). This requires additional routine blood samplings to comply with the USPI, i.e. complete blood count (CBC) with differential at least at screening, Month 6, Month 14, and Month 18. The USPI-required Month 2 sample may be covered by the LP-aligned Week 10 sample. The additional routine blood samples can be evaluated locally for ALC and other CBC parameters per routine practice at the respective site.

Clinical outcomes (Sections **Error! Reference source not found.** and **Error! Reference source not found.** of the study protocol) will be assessed at baseline, Week 5, Week 10, Months 6, 9,

and 12 during Year 1, and at Months 14, 18, 21, and 24 during Year 2 (see SoA in Section 1.3 of the study protocol).

MRI scans will be performed at screening, Month 12, and Month 24. All scans will be assessed centrally (Section **Error! Reference source not found.** of the study protocol).

Optional, exploratory single cell RNA sequencing of CSF and blood cells may be performed locally at each site, if sufficient CSF and blood sample material is available (Section **Error! Reference source not found.** of the study protocol).

In addition, RNA samples will be stored for future analysis from all study participants who consent to an optional RNA sample banking (Section **Error! Reference source not found.** of the study protocol).

Participants receiving a vaccine as standard of care and have started cladribine tablet treatment, will be given the opportunity to provide additional blood samples to examine antibody titers (see Section 8.9).

Visit schedules for all laboratory, efficacy, and safety assessments are detailed in the SoA (see Section 1.3 of the study protocol). If the start of cladribine tablets Year 2 treatment needs to be delayed (e.g. to allow for lymphocyte recovery to ≥800 cells/µL), all following visits and procedures, including any LPs and LP-aligned blood samplings, will be postponed by the same period of time (for up to 6 months), to maintain the protocol-specified time interval between start of cladribine tablets Year 2 treatment and all following assessments.

2.2.2 Randomization

Randomization will be conducted in REDCap with the randomization schedule generated by the study statistician. Randomization will be stratified by site and use block sizes of 4 within each strata.

Study participants will be randomized 1:2:2:1 (approximately 9:16:16:9 participants planned) to receive a total of 2 LPs according to 1 of the 4 following schedules:

1. Group 1: Baseline (Day 1) and end of Week 5 (LP to take place same day following intake of the last cladribine tablet of the first treatment course), or
2. Group 2: Baseline and end of Week 10, or
3. Group 3: Baseline and end of Year 1 (at least 43 weeks, but no later than 47 weeks, after the last tablet of the second cycle of cladribine Year 1 treatment), or
4. Group 4: Baseline and end of Year 2 (at least 43 weeks, but no later than 47 weeks, after the last tablet of the second cycle of cladribine Year 2 treatment).

Note: If the start of cladribine tablets Year 2 treatment needs to be delayed (e.g. to allow for lymphocyte recovery to ≥800 cells/µL), the end of Year 2 LP will be postponed by the same period of time (for up to 6 months), to maintain the protocol-specified time interval between start of cladribine tablets Year 2 treatment and the second LP.

In addition, all study participants randomized to Groups 1-3 can volunteer for a third, optional LP at the end of Year 2, the timing of which would be aligned with the second LP of Group 4.

2.2.3 Sample Size

The sample size for this hypothesis-generating study was based on the feasibility of enrollment. A sample size of 42 study participants is considered sufficient to describe the changes in CSF and serum biomarkers during treatment with cladribine tablets and to perform the exploratory modeling analyses to identify potentially predictive CSF or serum biomarkers. Assuming 15% of study participants will drop out during the 2-year study duration, a total of 50 participants who meet all inclusion and exclusion criteria will need to be randomized and dosed to have at least 42 participants who complete the study with all assessments performed.

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

2.2.4 Statistical interim analyses

This study is an open-label, single arm study with participants randomized to LPs at specific study time points to balance among participant at the different assessment time points. The study design creates multiple independent cohorts that can be evaluated for changes in the primary outcome. The comparisons within group between baseline and a specific time point are termed as interim analyses in the protocol and SAP as these analyses are being conducted on current data from an on-going study to address the primary research question. These interim analyses are not intended to modify the study conduct (e.g. stopping the study or changing the number of participants) and will not need to be adjusted for evaluating multiple hypothesis tests. All participants will complete the time point before analyses will be conducted.

The first interim analysis will be performed after Group 1 and Group 2 participants have completed their second LP (after Week 10).

- The analysis of the Week 5 LP data (Group 1 participants) is expected to provide information on the concentration of cladribine in the CSF.
- The data from the Week 10 LP (Group 2 participants) will provide information on the early impact of cladribine on neuronal injury and immune markers in the CSF at the time of the expected nadir of immune cell counts.

The second interim analysis will be performed after Group 3 participants have completed their second LP (after Month 12), to evaluate the persistence of effects of cladribine tablets in the CSF.

2.2.5 Stopping guidance

This is a Phase IV study so no stopping criteria are included in the protocol. The DSMB meets every 6 months and will continue to monitor for any safety concerns that might warrant stopping the trial early.

2.2.6 Timing of final analysis
The final analysis, including the analysis of the primary outcome, will take place after all participants have been recruited and followed for 24 months with all data entered and reviewed within the REDCap database.

2.2.7 Timing of outcome assessments
Timing of protocol assessments may be found in SoA (Section 1.3) within the study protocol.

2.3 Trial Population
Eligibility criteria can be found within the study protocol, Section 5.

2.3.1 Randomized analysis set
The randomized analysis set will be comprised of all participants that have been randomized to a lumbar puncture time point.

2.3.2 Randomized and treated analysis set
The randomized and treated analysis set will be comprised of all participants that have been randomized and receive at least one cladribine 10 mg tablet, regardless of adherence to the protocol. This includes participants who do not receive the study intervention (LP) as intended, have discontinued use of cladribine tablets, or those who are found to have been included in the study erroneously. Data from participants who have withdrawn consent for the study will be included in the analysis, unless they have specified that their data not be used. The analysis of all endpoints, unless otherwise noted, will be conducted using the randomized and treated analysis set as this is a Phase IV mechanistic study.

2.3.3 Safety analysis set
The safety analysis set will include all participants who receive at least one cladribine 10 mg tablet.

2.3.4 Interim analysis set
The interim analysis set will include the participants in the randomized and treated analysis set who were randomized to the specific lumbar puncture time point being considered. Interim 1 analysis set will include those participants randomized to the Week 5 and 10 LP time point while interim 2 analysis set will include those randomized to the Year 1 LP time point.

3 Endpoints

3.1 Primary endpoints

The primary endpoints will be assessed in the CSF and evaluate the change in levels of CD3+ T lymphocytes, CD19+ B lymphocytes, and NfL from baseline to second LP for the interim analyses and, for the final analyses, all participants with an LP at Year 2.

3.2 Key secondary endpoints

The key secondary endpoints will be assessed in the CSF (where applicable) and blood to evaluate the change in their levels from baseline to second LP for the interim analyses and, for the final analyses, all participants with an LP at Year 2.

Endpoint	**Flow cell markers**
CD4+ T cells	%CD45+CD3+CD4+
CD8+ T cells	%CD45+CD3+CD8+
Plasmablasts	%CD19+CD38+CD27+
Natural killer cells	%CD45+CD335+
CD4+ Tregs	%CD4+CD25+CD127-
Monocytes (or CD14+ cells)	%CD14+
Memory B cells %	% CD20+CD27+
Transitional B cell %	%CD19+CD38+CD24+ (CSF) %SSClowCD3-CD14-CD56-CD19+CD20+IgD+CD10+CD27- (Blood)

3.3 Secondary endpoints

The following secondary endpoints will be reported and compared from baseline to second LP for the interim analyses and, for the final analyses, all participants with an LP at Year 2. Given the exploratory nature of the study, a false discovery rate correction will be applied for analysis of secondary endpoints.

- Cladribine concentrations in the CSF and serum
- Serum NfL levels
- Blood Cellular Markers (Number, %) such as CD3+ T cells and CD20+ B lymphocytes
- Clinical outcomes
  - Annualized Relapse Rate (ARR) over 24 months of treatment with cladribine tablets. Relapses, as defined by the protocol section 8.1.1, will be summed between baseline to Month 12 and Month 12 to Month 24.
  - Change in EDSS scores from baseline at Month 12 and Month 24
  - 6-month confirmed EDSS progression. Confirmed EDSS progression will be defined as a 1-point increase in the EDSS if the baseline EDSS was ≤5.0 and half point increase in the EDSS if the baseline EDSS was 5.5, confirmed at a subsequent time point.

- MRI findings at Month 12 and Month 24 compared to baseline:
  - Gd+ lesions
  - New or newly enlarging T2 lesions

3.4 Exploratory endpoints

The exploratory endpoints will be assessed in the CSF and serum and evaluate the change in levels of biomarkers from baseline to second LP for the interim analyses and, for the final analyses, all participants with an LP at Year 2.

Exploratory endpoints include, but not limited to, the following:

- Biomarkers related to inflammation
  - Immunoglobulins
  - Oligoclonal bands
  - Chemokines such as CXCL13
- Biomarkers related to neuronal injury or degeneration
  - NfH
  - Tau

3.5 Safety endpoints

The safety endpoints will report the occurrence of TEAEs, SAEs, and TEAEs leading to treatment discontinuation, the absolute lymphocyte count assessed per USPI, and complete blood cell count as assessed per routine clinical practice.

4 Statistical Analysis

This is an exploratory, hypotheses-generating study. No formal hypotheses are planned for this study.

4.1 General Principles

Statistical analyses will be summarized descriptively and presented in tables, figures and data listings. Continuous variables will be summarized with means, standard deviations, and two-sided 95% confidence intervals (CIs), if normally-distributed, or medians and range, if not normally-distributed. Categorical/discrete variables will be displayed as frequency tables with counts and percentages. Parametric assumptions underlining the models specified will be examined.

Although this is a multicenter study, it is not expected to enroll enough participants at each site to allow for within-site analyses. Therefore, participants' data will be pooled across sites for all analyses.

Formal inferential statistical analyses techniques will be discussed in subsequent sections of this SAP. 95% confidence intervals will be used for all measures, where applicable. P-values will be considered statistically significant at the two-sided α=0.05 level, unless noted otherwise.

All analyses and tabulations will be performed using SAS Version 9.4 or higher on a PC platform. Table, listings, and figures will be presented in RTF format. Upon completion, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

The number of subjects with missing data will be presented. Missing or invalid data will be generally treated as missing, not imputed, unless otherwise stated.

4.2 Adherence and protocol deviations

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

Study drug adherence will be assessed by the clinical data monitor by reviewing study drug diaries and the study drug dispensing and accountability logs. Participants that fail to comply with study procedures will be recorded as protocol deviations.

Protocol deviations are summarized and reviewed every 6 months by the DSMB. Major protocol deviations that may affect the analyses will be considered for exclusion from the final intent-to-treat and/or per-protocol analyses.

4.3 Participant enrollment and disposition

Patient enrollment by site will be tabulated by randomization group and overall. Patient disposition will be summarized overall and include number of patients screened, number of patients who were screen failures with reason, number of patients who consented, and number of patients who were randomized.

The summary will include the number and percentage of patients in each of the defined analysis populations in Section 2 above. In addition, frequency counts and percentages of patients' reported reasons for ending the study will be summarized.

4.4 Baseline patient characteristics

Demographic data will be summarized descriptively and presented in tables. The following variables will be collected for all subjects:

- Age
- Sex
- Race
- Ethnicity
- Year of First MS Symptoms

- Year of MS diagnosis
- MS Type

4.5 Medical history

Medical history data will be coded by system organ class and preferred term, using the MedDRA dictionary. Medical history will be summarized by body system for each study arm in the Safety Population. The table will be sorted in alphabetic order by system organ class, as well as by incidence and preferred term, and the statistics n and % will be presented by study arm where: n is the number of subjects who present at least one occurrence of the medical history and % is the percentage of subjects. The denominator used for calculating the percentages will be the total number of subjects included in the Safety Analysis set for each study arm.

4.6 Primary endpoint analysis

The CSF levels of CD3+ T lymphocytes, CD19+ B lymphocytes, and NfL will be summarized at baseline and the second LP for the interim analyses and, for the final analyses, all participants with an LP at Year 2. The primary endpoints will be analyzed at Week 5 and Week 10 (Interim Analysis 1), Month 12 (Interim Analysis 2), and Month 24 (final analysis). The absolute and percent change from baseline will be presented for each time point for CD3+ T lymphocytes, CD19+ B lymphocytes, and NfL levels in CSF. Normality assumptions will be verified using visual inspection of residuals, however, these data are not expected to be normally distributed. As such, the nonparametric Wilcoxon signed rank test will be used to compare assess the effect of cladribine on these biomarkers. The statistically significant rejection of the null hypothesis in this case will be interpreted as the median change in the biomarker from baseline (prior to starting cladribine) was greater than 0. If the normality assumptions are not violated with the data or transformations (e.g. log) do not violate the assumptions, a paired t-test may be utilized in the statistical analysis. For the final analysis, an exploratory analysis assessing multiple time points within person will be conducted using a linear mixed model with time treated categorically and allow for all time points and data to be included in the analysis. The change over time will be examined graphically and pairwise comparisons of time points performed.

The analysis will be performed in SAS using PROC UNIVARIATE or the PROC TTEST with the paired option if the data are transformed. The regression analysis for all participants over time will be performed using PROC MIXED in SAS with, when possible, a random intercept and an unstructured covariance model. If the parameters are not estimable (lack of model convergence) using an unstructured covariance model, then other covariance structures or ordinary least squares estimates of the slope and intercept will be performed. As the analyses are exploratory, all comparisons will be tested at the 0.05 significance level. The analysis will be conducted in the interim analysis populations and the randomized and treated population.

4.7 Secondary endpoint analysis

Analysis of CSF biomarker secondary endpoints will be conducted as described for the primary endpoints. Analysis of blood biomarker secondary endpoints will utilize the analysis method described for the exploratory final analysis, a linear mixed model to examine the percent change from baseline for all available time points. The change over time will be examined graphically and pairwise comparisons of time points performed. For serum NfL level, the values will also be

converted to z-scores based on published control cohorts. Spearman rank correlations will be used to examine the relationship between biomarkers, and between biomarkers and clinical and MRI endpoints. PROC CORR with the SPEARMAN option will be utilized in SAS to perform the correlation analysis.

The secondary clinical and MRI endpoints will be analyzed at Month 12 (Interim Analysis 2) and Month 24 (final analysis). Data will be summarized descriptively. The ARR over the 12- and 24-month periods will be presented, accompanied by the respective 95% CIs. The proportion (and 95% CI) of participants experiencing a relapse over the 12-month and 24-month periods will also be presented. The change in EDSS from baseline will be reported at Month 12 and Month 24. In addition, the 6-month confirmed EDSS progression will be assessed. The mean number of Gd+ and new or newly enlarging T2 lesions over the 12- and 24-month periods will be summarized descriptively. The proportion of participants with no Gd+ lesions will be presented together with the corresponding 95% CI.

4.8 Exploratory analyses

Analysis of CSF biomarker exploratory endpoints will be conducted as described for the primary endpoints. Analysis of blood biomarkers will be performed as described for the secondary endpoints. Spearman rank correlations will be used to examine the relationship between biomarkers, and between biomarkers and clinical and MRI endpoints. Any post-hoc or unplanned analyses performed not identified in the prospective SAP will be clearly identified as such.

4.9 Safety analyses

Safety endpoints for adverse events (occurrence of treatment-emergent adverse events, SAEs and TEAEs leading to treatment discontinuation) will be summarized using frequency tables. The effect of cladribine tablets on safety labs (ALC, white blood cell counts, hemoglobin, platelets, and hematocrit) at Week 5 and Week 10 as part of the Interim Analysis 1 will be also be summarized descriptively. PROC FREQ will be used to summarize adverse events and PROC MEANS will be used to summarize safety labs.

5 Conventions

The precision of original measurements will be maintained in summaries, when possible. Means, medians and standard deviations will be presented with an increased level of precision; means and medians will be presented to one more decimal place than the raw data, and the standard deviations will be presented to two more decimal places than the raw data.

Summaries of continuous variables that have some values recorded using approximate values (e.g., lab values < 0.001 or >200) will use imputed values. The approximate values will be imputed using the closest exact value for that measurement. For tables where rounding is required, rounding will be done to the nearest round-off unit. For example, if the round-off unit is the ones place (i.e., integers), values ≥ XX.5 will be rounded up to XX+1 while values < XX.5 will be rounded down to XX.

Percentages will be based on available data and denominators will generally exclude missing values. For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the patients discontinue due to

"lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.

6 Standard Calculations

Variables requiring calculation will be derived using the following formulas:

Study day – For a given date (date), study day is calculated as days since the date of first dose of study drug (firstdose):

Study day = date – firstdose + 1, where date ≥ firstdose

Study day = date – firstdose, where date < firstdose

Days – Durations, expressed in days between one date (date1) and another later date (date2), are calculated using the following formula:

duration in days = (date2-date1).

Weeks – Durations, expressed in weeks between one date (date1) and another later date (date2), are calculated using the following formula:

duration in weeks = (date2-date1)/7.

Months – Durations, expressed in months between one date (date1) and another later date (date2), are calculated using the following formula:

duration in months = (date2-date1)/30.4.

Years – Durations, expressed in years between one date (date1) and another later date (date2), are calculated using the following formula:

duration in years = (date2-date1)/365.25.

Minutes – Durations, expressed in minutes between one timepoint (time1) and another later timepoint (time2), are calculated using the following formula:

duration in minutes = (time2-time1)/60.

Age – The patient's age is calculated as the number of years from the subject's date of birth to the date of randomization into the study:

Age = ([Randomization Date - Date of Birth]/365.25).

7 Statistical Software

All analyses and tabulations will be performed using SAS Version 9.4 or higher on a PC platform. R Version 3.1 or higher may be used for statistical graphics.