Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS700568-0026
Title	Evaluating the Long-Term Outcomes and Durability of Effect Following Treatment with Cladribine Tablets for Multiple Sclerosis: An Exploratory Phase IV Ambispective Study of Patients Who Previously Participated in the CLARITY/CLARITY-EXT and ORACLE MS Clinical Trials
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Approval Page

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Merck Responsible	Date	Signature
PPD		

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2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Confidence Interval
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
DMD	Disease Modifying Drugs
EMA	European Medicines Agency
FAS	Full Analysis Set
FCDE	First Clinical Demyelinating Event
FDIMP	First Dose of Investigational Medicinal Product
GPP	Good Pharmacoepidemiology Practices
HDA	High Disease Activity
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IMP	Investigational Medicinal Product
IRB	Institutional Review Boards
IAP	Integrated Analysis Plan
KM	Kaplan-Meier
LDIMP	Last Dose of Investigational Medicinal Product
MedDRA	Medical Dictionary for Regulatory Activities
MRISS	MRI Sub-Study population
NA	Not Applicable
PD	Protocol Deviation
PT	Preferred Term

PGx	Pharmacogenetics
PSD1	Parent Study Day 1
SAE	Serious Adverse Event
SD	Standard Deviation
SDTM	Study Data Tabulation Model
SNP	Single Nucleotide Polymorphism
SOC	System Organ Class
SV1	Study Visit 1
TLF	Tables, Listings, and Figures
WHODD	World Health Organization Drug Dictionary
WPS	Whole Parent Study

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	May 13th, 2020	PPD	NA
2.0	June 15th, 2020	PPD	Clarification of analysis sets, addition of new responder definition, and other minor
3.0	November 10th, 2020	PPD	Updated following protocol amendment, addition of MRI parameters and minor update of the PGx section.

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed statistical specifications for the analysis of data collected for protocol MS700568-0026 called CLASSIC MS ("CLASSIC" is used interchangeably). 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 will be included in 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 (Statistical Considerations) of the study protocol and is prepared in compliance with International Conference on Harmonization (ICH) E9 and Guidelines for Good Pharmacoepidemiology Practices (GPP). It describes analyses planned in the protocol.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To evaluate long-term mobility after treatment with an investigational medicinal product (IMP; Cladribine Tablets or placebo) as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Proportion of study participants using a wheelchair (defined as unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day) the majority of the time in the 3 months prior to Study Visit 1 (SV1) or participants are bedridden any time prior to SV1, determined via: 1) Expanded Disability Status Scale (EDSS) score of 2) 7.0 or higher), or Alternative clinical description data in medical records.	Section 14.1
Secondary		

Objectives	Endpoints (Outcome Measures)	IAP section
To assess the long-term disability status after treatment with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Proportion of study participants with EDSS of 6.0 or higher as determined by EDSS documentation or alternative clinical description in medical records after last IMP from parent study.	Section 14.2.1
To evaluate differences in clinical characteristics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Clinical characteristics[a] at Study Visit 1 of long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to those of other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Section 14.2.2
To evaluate differences in magnetic resonance imaging (MRI) characteristics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	MRI characteristics[c] at Study Visit 2 of long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to those of other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Section 14.2.3
Tertiary		
To assess the real-world treatment patterns in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITYEXT clinical trials.	Time, type, and reason for first sequential treatment after first course[b] of IMP, type of second sequential treatment, as well as the frequency of routine clinical monitoring and disease activity status as well as clinical and demographic characteristics[a] available for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Section 14.3.1

Objectives	Endpoints (Outcome Measures)	IAP section
To assess durability of clinical outcomes after treatment with IMP from Baseline (i.e. first dose of IMP) to Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Tertiary endpoints to be evaluated via retrospective data collection from medical records or at Study Visit 1: • Proportion of study participants being bedridden[d] • Time from first dose[b] of IMP to first use of an ambulatory device[d] • Time from first dose[b] of IMP to first use of a wheelchair[d] • Annualized Relapse Rate (ARR) from time of first dose of IMP to Study Visit 1, and by 2-year intervals • Time to conversion to Clinically Definite MS (CDMS) (For ORACLE MS study participants only) • Proportion of study participants diagnosed as Secondary Progressive MS (SPMS) without relapses in the 3 months prior to SPMS diagnosis • Proportion of study participants diagnosed as SPMS with relapses in the 3 months prior to SPMS diagnosis • Proportion of study participants diagnosed as Primary Progressive MS (PPMS) (For ORACLE MS study participants only)	Section 14.3.2
To assess impact on quality of life and cognitive outcomes after treatment with IMP during the period from the last clinical visit in the CLARITY/CLARITYEXT/ ORACLE MS clinical trials to Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	Tertiary endpoints to be evaluated at Study Visit 1: • Change in EuroQoL-5 Dimension Questionnaire (3 level version) (EQ-5D-3L) • Change in cognition as measured by the following assessments (to be collected for ORACLE MS subjects only in countries where these instruments were used in the CLASSIC MS study): • The Brief Visuospatial Memory Test – Revised (BVMT-R) • Symbol Digit Modality Test (SDMT)	Section 14.3.3
To assess durability of outcome on brain imaging after treatment with IMP from Baseline (i.e. the last MRI before first dose of IMP; if feasible, by year) to within 3 months after Study Visit 1 in study participants previously treated with IMP as part of the Phase III ORACLE MS and CLARITY/CLARITY-EXT clinical trials.	ORACLE MS, CLARITY and CLARITY-EXT study participants from selected sites will be invited to participate in a follow-up study visit (Study Visit 2) to take place within 3 months (maximum 4 weeks from Visit 1 after last patient enrolled) following Study Visit 1, for evaluation of the following: Change in MRI assessment from Baseline (i.e. the last MRI before first dose[b] of IMP) to Study Visit 2 in: • Total volume of T2 lesions • Total number of T2 lesions • Number of hypointense lesions on T1-spin echo MRI • Volume of hypointense lesions on T1-spin echo MRI • Brain volume or surrogate (in cases where brain volume is not possible to assess for technical reasons, then 3rd ventricle diameter may be evaluated) • Ventricular volume	Section 14.3.4

Objectives	Endpoints (Outcome Measures)	IAP section
To determine whether the high-disease activity (HDA) patients from the CLARITY/CLARITY-EXT clinical trials are more likely to be the long-term responders.	Comparison of the responder rate in HDA patients[e] versus the responder rate in non-HDA patients from the CLARITY/CLARITY-EXT population.	Section 14.3.5
To evaluate differences in genetics between long-term responders and study participants requiring alternate therapies following treatment with IMP for the CLARITY/CLARITY-EXT and ORACLE MS populations.	Correlation of genetic variations with long-term responders (defined as study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes until Year 4 or later following their last dose[b] of IMP and who did not receive disease modifying treatment until Year 4 or later following their last dose[b] of IMP) compared to other study participants who started on alternate therapy less than 4 years following their last dose[b] of IMP for the CLARITY/CLARITYEXT and ORACLE MS populations.	Section 14.3.6

[a] Specific clinical and demographic characteristics may include gender, age, race, ethnicity, education, disease duration, years previous disease modifying treatment (before start of CLARITY/CLARITY-EXT/ORACLE MS) and disease classification (RRMS or SPMS).
[b] One dose is equivalent to one tablet. One course of IMP is defined as 1 year of treatment with IMP (2 treatment cycles [weeks]). A treatment cycle is defined as daily administration of IMP given consecutively over 4-5 days during a 28-day period. One treatment week is equivalent to 1 treatmentcycle.
[c] Total volume of T2 lesions; Total number of T2 lesions; Number of hypointense lesions on T1-spin echo MRI; Volume of hypointense lesions on T1-spin echo MRI; Brain volume orsurrogate; Ventricular volume.
[d] Mobility endpoints may be determined via EDSS scores (if available) or corresponding clinical descriptions in medical records.
[e] 1. Patients with ≥2 relapses during the year prior to parent study entry, regardless of prior disease modifying drugs (DMD) use; 2. Patients with ≥1 relapse in the previous year and ≥1 T1 Gd+ lesions or ≥9 T2 lesions, while on therapy with other DMDs.

6 Overview of Planned Analyses

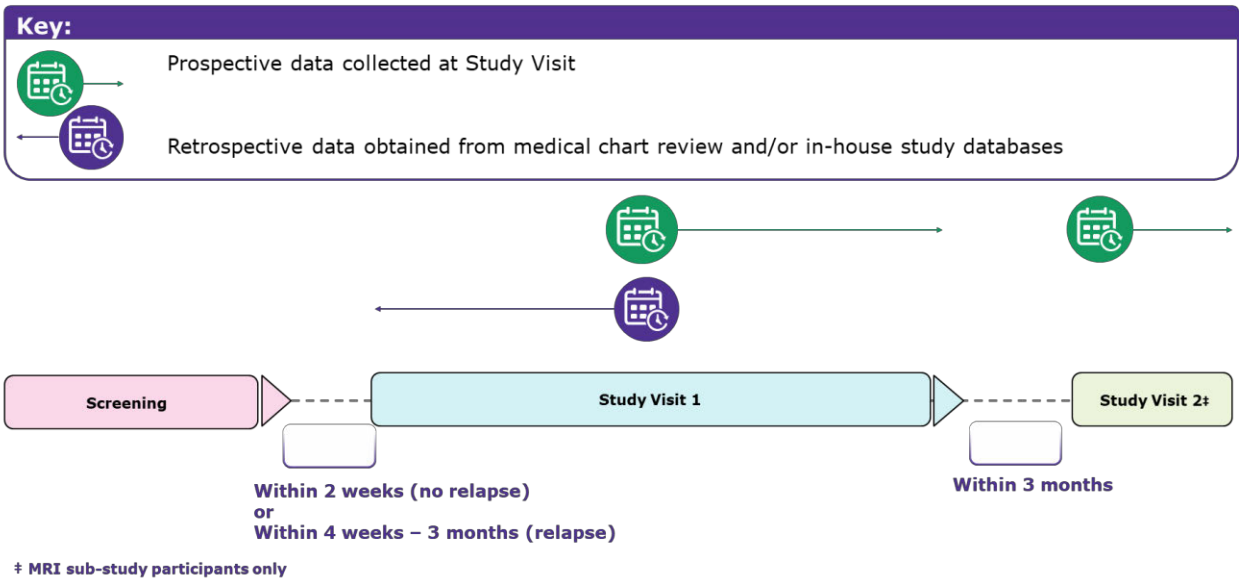
6.1 Summary of CLASSIC MS

This Phase IV, low-interventional, multicenter, ambispective study will involve the evaluation of medical records of study participants treated with Cladribine Tablets or placebo (IMP) in the previously conducted parent studies. Long-term retrospective data will be collected through evaluation of medical charts/records, and additional prospective data will be collected. No IMP will be administered as part of this study. A total of 1943 patients has been enrolled in the parent studies, 1326 from CLARITY (including 867 enrolled in CLARITY-EXT) and 617 from ORACLE MS. This study will collect data from study participants with MS who participated in the CLARITY/CLARITY-EXT clinical trial(s) and who received ≥ 1 course of IMP, or study participants with their First Clinical Demyelinating Event (FCDE) who were randomized in the ORACLE MS study and received ≥ 1 course of IMP.

Participants are invited to up to 3 clinic visits for this study. The first visit is the Screening Visit.

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

Figure 1: CLASSIC study Overview Diagram



6.2 Summary of Parent Studies

CLARITY (25643): The CLARITY (CLAdRIbine Tablets treating MS orallY) study was a multicenter, randomized, double-blind, three treatment group study of 96 weeks duration. Depending on their body weight, subjects took 1 or 2 cladribine 10 mg tablets (or matching placebo) per day over 4 to 5 days in either (a) Week 1 and Week 5 of Years 1 and 2, or (b) in Weeks 1, 5, 9, and 13 of Year 1, followed by Weeks 1 and 5 of Year 2, for a cumulative dose of 3.5 and 5.25 mg/kg, respectively. The primary objective of the trial was to evaluate the efficacy of cladribine versus placebo in the reduction of qualifying relapse rate during 96 weeks of treatment in subjects with RRMS. The secondary objectives were to assess the effect of cladribine on progression of disability (EDSS) and lesion activity as measured by MRI.

CLARITY EXT (27820): The CLARITY EXT (CLAdRIbine Tablets treating MS orally EXTension) study was a randomized, double-blind, 96-week Extension study to evaluate the long- term safety and efficacy of oral cladribine in subjects with RRMS who had completed the CLARITY study. In the CLARITY EXT study, only the lower dose of cladribine was administered (subjects took 1 or 2 cladribine 10 mg tablets (or matching placebo) per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2, for a cumulative dose of 3.5 mg/kg). Subjects who were assigned to the placebo arm in CLARITY were assigned to cladribine treatment. Subjects who received cladribine in CLARITY were randomized to either placebo or cladribine 3.5 mg/kg treatment groups in a 1:2 ratio, creating 5 arms:

Cladribine high/low dose (HLLL): Subjects who were randomized to cladribine high dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Weeks 1, 5, 9, and 13 of Year 1, followed by Weeks 1 and 5 of Year 2 of the CLARITY study (25643) (total dose 5.25 mg/kg), and to cladribine low dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2 of the CLARITY extension study (total dose 3.5 mg/kg).

Cladribine low/low dose (LLLL): Subjects who were randomized to cladribine low dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2 of the CLARITY study (25643) (total dose 3.5 mg/kg), then to cladribine low dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2 of the CLARITY extension study (total dose 3.5 mg/kg).

Cladribine high/placebo (HLPP): Subjects who were randomized to cladribine high dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Weeks 1, 5, 9, and 13 of Year 1, followed by Weeks 1 and 5 of Year 2 of the CLARITY study (25643) (total dose 5.25 mg/kg), and then to placebo for the years 1 and 2 of the CLARITY extension.

Cladribine low/placebo (LLPP): Subjects who were randomized to cladribine low dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2 of the CLARITY study (25643) (total dose 3.5 mg/kg), then on placebo for the years 1 and 2 of the CLARITY extension study.

Placebo/Cladribine low dose (PPLL): Subjects who were randomized to placebo for the first and second year of CLARITY study (25643), then to cladribine low dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2 of the CLARITY extension study.

Due to administrative reasons, there was a varying period (median time 41 weeks, range 1 day to 118 weeks) between a subject completing the CLARITY study and starting in the CLARITY EXT study, subjects did not receive cladribine during this time period. Following the end of the 96-week CLARITY EXT study period, subjects were followed for safety for an additional 24 weeks. The primary objective of this trial was to evaluate the safety of extended treatment with oral cladribine when administered to subjects who completed CLARITY (25643).

ORACLE MS (28821): The ORACLE MS (ORAl CLadribine in Early MS) study was a Phase III, randomized, double-blind study to evaluate the safety and efficacy of oral cladribine tablets as a monotherapy in subjects at risk of developing MS (subjects who have experienced a first clinical event suggestive of MS). Subjects were randomized to either oral cladribine high dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Weeks 1, 5, 9, and 13 of Year 1, followed by Weeks 1 and 5 of Year 2 (total dose 5.25 mg/kg), or oral cladribine low dose with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2 (total dose 3.5 mg/kg), or matching placebo. The design was a time-to event design with treatment schedules dependent on conversion to clinically definite multiple sclerosis (CDMS) according to the Poser criteria at any time during the first 96 weeks:

Subjects who converted to CDMS according to the Poser criteria at any time during the first 96 weeks (i.e., during the double-blind period) stopped the blinded study drug and entered an open-

label maintenance period, where they were offered open-label IFN-β and underwent evaluations for safety and efficacy.

All other subjects were planned to continue their blinded treatment up to the end of the first 96 weeks double-blind period (end of Year 2).

At the end of the first 96 weeks double-blind period, McDonald MS 2005 was assessed for all subjects and treatment schedules depended on the outcome:

- Subjects who converted to McDonald MS criteria were allocated to receive open-label oral cladribine (3.5 mg/kg) administered with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2 (total dose 3.5 mg/kg) of the extension phase.

- Subjects who did not convert McDonald MS criteria at end of Week 96 were to be followed without treatment.

- At any time during the Extension phase, open-label cladribine with 1 or 2 cladribine 10 mg tablets per day over 4 to 5 days in Week 1 and Week 5 of Years 1 and 2 (total dose 3.5 mg/kg) if conversion to McDonald MS criteria or IFN-β (if conversion to CDMS) may have been used following the rule above.

The ORACLE MS was terminated earlier than planned in October 2011. No further dosing of blinded study medication or open-label cladribine was allowed (open-label IFN-β was offered for subjects who converted to McDonald MS). Subjects were to complete the end of trial visit assessments after a safety follow-up period of 24 weeks from the time of last dose of blinded study medication or open label cladribine.

6.3 Source Database

This analysis will use SDTM and ADAM data of each of the parent study and SDTM data of the CLASSIC study. At the time of this working document all parent studies were completed.

6.4 Interim Analyses

An interim analysis was planned to publish results when data from 50% (100 is minimum required) patients were available from cohort A (see section 8.1 for definition of Cohort). This data included the primary and selected secondary endpoints (or their components) as well as the EQ-5D-3L analysis (see Section 14 for further details on analyses and appendix 17.1for outputs provided); pharmacogenetics and MRI were not planned to be included in the interim analysis. Results of the interim analysis have been disseminated per dissemination plan of the study, but no formal study report has been written.

6.5 Final Analysis

All analyses described in this IAP will be performed after the final database lock (see Section 14

for further details on analyses) and summarized in final study report. Results of the final analysis will be summarized in a formal study report.

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the analyses planned per protocol.

8 Analysis Populations and Subgroups

8.1 Definition of Analysis Populations

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

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

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

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

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

The parent study identification is specified in the demographic eCRF page and will be used to identify cohort. If the parent study identification is missing, then the participant will not be included in any cohorts/analysis.

Patients will be analyzed according to their actual exposure/no exposure to oral Cladribine in the parent study. For Oracle patients, treatment during initial treatment period and open label are used for this categorization.

8.1.1 Full Analysis Set

The full analysis set (FAS) will include all patients participating in CLASSIC study (randomized in CLARITY and have received ≥ 1 course of IMP [Cladribine Tablets or placebo] or patients randomized in the ORACLE study and have received ≥ 1 course of IMP).

Patient who have received ≥ 1 course of IMP will be identified using a list of patients provided to sites by the sponsor. Patients enrolled in the study but did not complete 1 course of IMP will be considered protocol deviation.

There will be no per-protocol analysis population excluding patients with protocol deviations.

8.1.2 The MRI Sub-Study Analysis Set (MRISS)

The MRI Sub-Study Analysis population includes all FAS participants who signed the MRI sub-study informed consent (Optional Informed Consents eCRF page).

The MRISS population will be used on second and tertiary endpoints related to MRI analysis. Please see section 14 for further details.

8.1.3 The Whole Parent Study population (WPS)

The WPS population include all parent study patients (enrolled in CLASSIC or not) randomized in CLARITY or ORACLE who have received ≥ 1 course of IMP (Cladribine Tablets or placebo) *. The WPS population will be used to evaluate potential selection bias described in Section 9 of the protocol. This population will exclude CLASSIC patients who did not receive ≥ 1 course of IMP (important protocol deviations).

*One course of IMP is defined as 2 treatment weeks. A treatment week is defined as daily administration of IMP given consecutively over 4-5 days during a 28-day period.

8.1.4 The pharmacogenetic population (PGX)

The PGX population includes all FAS participants who signed the informed Consent for optional pharmacogenetic testing (Optional Informed Consents eCRF page) and provided suitable blood sample.

8.2 Subgroup Definition and Parameterization

8.2.1 Parent Study Treatment groups

Analyses will be performed on the "as treated principle", where patients are allocated to the treatment that they actually received in the parent study (which may be different from the study treatment to which they were randomized to).

- **Parent study never exposed to cladribine**: if a subject has taken only placebo in all studies, then her/his data becomes part of the "Never exposed to cladribine" parent study treatment group. A subject who switches treatment from placebo to cladribine in subsequent studies/periods **will not** be considered in this group.

- **Parent study exposed to cladribine**: patients with at least one dose of cladribine. Subjects who were on placebo during the clinical trial and switched to cladribine in the extension study will contribute to the parent study treatment group “Exposed to cladribine”.

For Oracle patients, treatment during initial treatment period and open label are used for this categorization.

8.2.2 Subpopulations

Subgroup analyses will be performed on primary, secondary and tertiary efficacy endpoints as defined in section 14. All subgroup analyses will be exploratory and descriptive in nature.

In case of low number of participants within a category (< 25% participants by subgroup categories), subgroup analysis for that variable will not be performed.

Subgroups analyzed are:

1. Subgroup Treatment Course in Cohort B
2. Long-term Responder/Non-responder (4 definitions)
3. Subset Types of Subsequent DMDs
4. Subgroup Prior Use of DMD for cohort B
5. Subgroup HDA for Cohort B

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

1. **Subgroup Treatment Course in Cohort B:**

   a) **Placebo:** Study participants who received placebo only (i.e. study participants that received placebo in CLARITY who did not enter CLARITY-EXT, or received placebo in both CLARITY and CLARITY-EXT)
   b) **1 treatment course (year) of Cladribine:** Study participants who received at least 1 dose of Cladribine Tablets during either CLARITY or CLARITY -EXT but did not start the 2nd year treatment courses of Cladribine Tablet.

   c) **2 treatment courses (years) of Cladribine:** Study participants who received at least 1 dose of Cladribine Tablets during either CLARITY or CLARITY -EXT that started the 2nd year treatment courses of Cladribine Tablets but did not started a third-year treatment course of Cladribine treatment.

   d) **More than 2 treatment courses (years) of Cladribine:** Study participants who received at least 1 dose of Cladribine Tablets during CLARITY and CLARITY -EXT that started > 2 treatment courses of Cladribine Tablets (i.e. patients who completed CLARITY and started at least the 1st year treatment courses in CLARITY-EXT). This corresponds to participants who completed 2 courses of Cladribine treatment and started the third course of Cladribine treatment.

Computation rules:

The above groups will be determined based on how many treatments years participant had in the parent study:

Year 1: From first Cladribine dose date to End of Year 1.
End of Year 1 is defined as the day of the earliest exposure greater or equal to year 1 start date + 308 days

To define (b), (c) and (d): If at least 1 dose of Cladribine has been administered after end of Year 1, for CLARITY or CLARITY EXT then the participant will be considered starting the second treatment course (year). If at least 1 dose of Cladribine has been administered during the first year of CLARITY EXT after receiving at least 1 dose during the second treatment course of CLARITY, then the participant will be considered starting the third treatment course (year). Individual parent study datasets will be used.

2. Long-term Responder/Non-responder:

a. Primary definition

- **Long-term Responder:** Study participants not requiring DMD 4 years or later following their last dose of IMP, and who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes

- **Non-Responder**: Study participants requiring DMD less than 4 years following their last dose of IMP or who demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes.

Computation rules:

Prior/concomitant medication eCRF page and "physician sequential treatment decision questions" eCRF page question 8 and 9 to be used to identify the date of the DMD received.

4 years after last dose of IMP = Last dose of IMP date + 4*365.25 days

Evidence of disease reactivation will be defined by either:

a) MRI lesions: new T1 lesion or new T2 lesion reported
b) New Relapse reported
c) EDSS worsening defined as an EDSS score increase of at least 1 point between 2 consecutives visits of at most 365 days (if 2 consecutive EDSS assessments are separated by more than 365 days then EDSS cannot be used in the criteria and will be considered as missing/not reported).

New relapse, MRI lesions and EDSS worsening will be identified utilizing dates in parent studies for the period between last dose of IMP and end of parent study.

For the period following the end of the parent study until SV1 of Classic study the following source data will be used:

1) MRI lesion by the eCRF "frequency stable patient monitoring questions" (fspmq) page,

Q4/Q3. If Q4 is answered "yes" the date will be taken from Q3 and determined if the MRI lesion is before the 4 years since last IMP.

2) New relapse will be identified using the eCRF "MS Relapse history" page(hxrelap) Q2.2.

3) The EDSS worsening by the eCRF "expanded disability status scale (edssr) for retro data" page.

All partial dates will be imputed as described in Section 9.5.

Different scenarios considering missing/not collected data are provided in the table below:

DMD required	MRI new lesion	New Relapse	EDSS worsening	Responder (Yes/No/ND)
All are missing				ND
At least one is Yes (with or without missing)				No
All are N (with no missing)				Yes
All are N (with at least one missing)				ND

ND=Not determined

b. Definition B (sensitivity):

- **Long-term Responder:** Study participants not requiring DMD 4 years or later following their last dose of IMP.
- **Non-Responder**: Study participants requiring DMD less than 4 years following their last dose of IMP.

c. Definition C (sensitivity)

- **Long-term Responder:** Study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes 4 years following the last dose of IMP.
- **Non-Responder**: Study participants who demonstrate any evidence of disease reactivation based on Investigator assessment of clinical and imaging outcomes 4 years following the last dose of IMP.

d. Definition D (sensitivity)

- **Long-term Responder:** Study participants who did not demonstrate any evidence of disease reactivation based on Investigator assessment of clinical outcomes 4 years following the last dose of IMP.

- **Non-Responder**: Study participants who demonstrate any evidence of disease reactivation based on Investigator assessment of clinical outcomes 4 years following the last dose of IMP.

Definition A described above is considered the primary definition and will be used in the final analysis. Definition B (definition A revised, using DMD only), Definition C (definition A revised, using reactivation of disease only), and Definition D (as C but removing MRI criteria) will be also performed as a sensitivity analysis. MRI lesions or retro EDSS information are expected to be missing/not collected/not reported. Additional descriptive statistics will be provided for each of the component used in the definition to assess the validity of the criteria.

3. **Subset Types of Subsequent DMDs:**

- Platform injectable therapy (Interferon-β [Avonex®, Rebif®, Betaferon®, Extavia®, Plegridy®] or glatiramer acetate [Copaxone®])
- Monoclonal antibody disease modifying treatment
- Oral disease modifying treatment
- Other subsequent treatment
- Off-label treatments (drugs not approved by regulatory agencies to treat MS)
- No subsequent treatment

Subsequent DMD groups will be identified using a DMD medication lookup list provided by the coding team and reviewed by the medical team. This DMD list will be looked vs all medications reported in prior/concomitant medications, Physician Sequential Treatment Decision eCRF page question 8 in CLASSIC and parent study data. The first subsequent DMD after last dose of IMP will be used to define the subset.

4. **Subgroup Prior Use of DMD for cohort B:**

- Prior Use of DMD at any time in the patient's history before enrolment into CLARITY
- Complementary subgroup

Prior use of DMD will be identified using same approach described for subsequent DMD using parent study data.

5. **Subgroup High Disease Activity for Cohort B:**

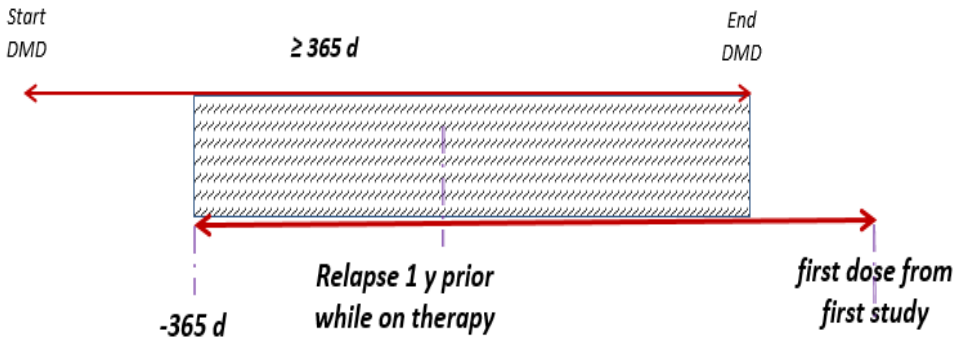
The definition of HDA will be similar to regulatory submission, programs from EMA CSE, will include patients from CLARITY study, and subgroups will be identified using parent study data.

HDA is defined by:

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

Non-HDA is the complementary group.

Table 1: High Disease Activity Definition details

Patients in the previous year while on DMD therapy	DMD are medications with preferred term defined in section 12of the iAP. If more than 1 DMD is used, only last DMD (the closest to Parent Study Day 1 [PSD1]) is considered. Collected start/end date of prior DMD is used to compute prior DMD treatment duration. If end date after PSD1, duration is truncated to PSD1-1. When start/end date are partial (day or month or year missing), imputation rule as described in section 9.5of the iAP is followed.
Patients should have at least 1 relapse in the previous year while on therapy	≥1 relapse in previous year while on therapy. While on therapy is calculated as follows: If duration of DMD treatment is ≥365 days and end date is within 1 year of PSD1, then relapses are considered "while on therapy", if occurring in time period coinciding with DMD therapy. Graphical Representation of Relapse while on therapy  Data processing/Handling of partial dates: Relapses with partial onset date are imputed as follows: • Missing day will be imputed to be 15 and missing month will be imputed to be June. • No imputation for complete missing date. Relapses are collected when associated with a date. If no date of relapse is reported, number of relapses is set to 0 (zero).
and have at least 9 T2-lesions	≥9 Total T2 lesions prior to first study. Handling of missing data: If T2 lesion is missing prior to first study, subject is considered in the <9 T2 lesions.
or at least 1 Gadolinium-enhancing lesion	≥1 T1 Gadolinium-enhancing lesion prior to first study Handling of missing data: If T1 lesion is missing prior to first study, subject is considered in the <1 T1 Gd+ lesion.

8.3 Definition of Protocol Deviations

Important protocol deviations and Clinically important deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a participant's rights, safety, or well-being. These deviations are identified in appendix 17.3 (standalone document), confirmed at the protocol deviation review meeting, and are recorded in the database as such. There will be no separate per-protocol analysis for this study.

9 General Specifications for Data Analyses

9.1 Identification of patients

Patients are identified by their unique subject number taken from the subject ID in their parent study and matched with Classic ID using pre-specified demographic data. If a patient is not matching on at least one demographic variable, this patient will not be included in the analysis.

Table 2: Identification

Unique Subject Identifier	First Previous Study	Previous Clinical Trial
00000256430060001	25643	CLARITY only
00000256430020001	25643	CLARITY/CLARITY EXTENSION
00000288218640003	28821	ORACLE MS

9.2 Dictionary coding

The Adverse events (AEs) and Medical History will be coded with MedDRA v22.1 or higher. Concomitant medications will be upgraded with WHO Drug Dictionary version 2019-September or higher.

9.3 Timepoints

- **Date of First dose of IMP (FDIMP)** is the day of start of first study drug intervention (placebo or cladribine).
- **Date of Last dose of IMP (LDIMP)** is the day of end of study drug intervention (placebo or cladribine). For ORACLE patient both ITP and open label period will be observed to identify the end of study drug intervention.
- **The end of the parent study** is defined as the last date of data collection from the parent study.

- **Baseline** (of parent study) is defined as PSD1 baseline, which is the last assessment prior to or at FDIMP.

9.4 Conversion factors

The following conversion factors will be used:

- 1 year = 12 months = 365.25 days
- 1 month = 30.4375 days

9.5 Handling of missing data/ Presentation of continuous and qualitative variables

It is anticipated that missing/not reported data will feature many of the endpoints, especially BVMT-R and SDMT (see section 14.3.3). No imputation will be done for these assessments.

In general, missing or partial dates will be imputed as follows:

- If year and month available but day is missing, impute day to 15
- If only year available, impute day and month to 15JUN
- If date is completely missing, then no imputation will be done, except for Concomitant Medication end dates: if end date is completely missing (day, month and year) and partial or complete start date then end date will be imputed to be the last study assessment date.

In addition, for concomitant medication dates:

- If imputed start date is after end date, then the start date will be set equal to end date.

- If imputed end date is before start date, then the end date will be set equal to start date.

For time to event analyses, if partial date does not determine whether event occurred before or after start date, then analysis date will be set equal to start date, subject will be censored and time to censoring = 1/365.25.

Continuous variables:

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

- number of subjects (N),
- number of subjects with non-missing values,
- number of subjects with missing values
- mean and standard deviation,

- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum, and maximum.

Qualitative variables:

Qualitative variables will be summarized by counts and percentages.

There are no plans for any formal statistical inference. This study will adhere to the Guidelines for Good Pharmacoepidemiology Practices (GPP). Data evaluation and interpretation will be based on point estimates and 95% corresponding confidence intervals (CI). Due to the exploratory nature of the study, an adjustment for multiple comparisons is not required.

Analyses will be performed using SAS® Software version 9.4 or higher.

10 Study Participants

The subsections in this section describe the specifications for reporting participant disposition and study discontinuations.

10.1 Disposition of Participants and Discontinuations

Number of subjects screened, number of subjects by parent study treatment group ("never exposed to Cladribine" and "exposed to Cladribine") will be presented by cohort (A, B, C and D).

Study status (CLASSIC and parent study) will be summarized by cohort, presented as Completed or Discontinued.

Reason for study discontinuation will be summarized.

Time since end of parent study, time since first dose and time since last dose will be summarized in weeks as a continuous variable and in years as categorical for time intervals and in cumulative time intervals with the following categories:

Table 3: Time intervals

Cumulative intervals	**Time intervals**
Less than 5 years	1 to 1826 days (260 weeks, 5y)
At least 5 years	1827 to 3652 days (521 weeks, 10y)
At least 10 years	3653 to 5478 days (782 weeks, 15y)
At least 15 years	5479 to 7305 days (1043 weeks, 20y)
Etc.	Etc.

10.2 Protocol Deviations/Exclusion from Analysis Populations

Important protocol deviations and Clinically important deviations will be summarized by type of deviation and listed.

11 Demographics and Other Baseline Characteristics

11.1 Demographics

Summaries will be presented by parent study treatment group and total, repeated for each cohort.

The following variables will be based on FDIMP.

- Age at Study Visit 1, continuous years and in categories (<= 50 y, >50 y)
- Age at parent study baseline, continuous years and in categories (<= 50 y, >50 y)
- Sex (male, female)
- Race: (White, Black or african american, Asian, Other), other include american indian or Alaska native
- Region: America US, America non-US*, Western Europe, Australia, Eastern Europe, Russia, ROW

  *America non-US includes Canada and all countries from South America.
- Disease duration (years)
- Type of MS at screening
- Employment Status
- Education Level
- EDSS at parent studies baseline
- EDSS at Visit 1 (by phone, clinical [site] and their maximum)
- Number of relapses (for CLARITY patients only)
- Prior use of DMD (for CLARITY patients only)
- HDA status (for CLARITY patients only)
- Treatment courses in cohort B
- Long term responders definitions A, B , C, and D
- Type of first DMD after Last IMP dose

The number of subjects by region and country will be summarized on the FAS for each cohort.

Additional analysis:

Using WPS population, the following analyses will be performed to assess potential selection bias:

Comparison of baseline and disease characteristics between CLASSIC participant vs patients who did not participate in the CLASSIC study (and were eligible for CLASSIC study).

Baseline and disease characteristics (at parent study) considered are:

- Age
- Sex
- Region
- Race
- EDSS
- Number of relapses (for CLARITY patients only)
- Prior use of DMD (for CLARITY patients only)
- HDA status (for CLARITY patients only)

11.2 Medical History

The medical history will be summarized from the "Medical History details" eCRF page, using MedDRA, preferred term as event category and system organ class (SOC) body term as Body System category. Each participant will be counted only once within each PT or SOC.

Listing will also be provided.

12 Previous or Concomitant Medications/Procedures

Previous or concomitant medication will be presented based on FAS analysis set for Cohort A and will be presented by ATC and Preferred Name, per parent study exposed group and total. Listing will also be provided.

Previous and concomitant medications are medications, other than parent study medications (i.e. cladribine or placebo), which are taken by patients any time on-trial before or on or after CLASSIC Study Visit 1.

Handling of missing or partial dates are critical for medications identified as DMD that will determine timing of DMD in responders/non-responders and prior DMD use variables. All missing/incomplete dates will be imputed as described in Section 9.5.

Medications in CLASSIC

Medications in CLASSIC are medications which are taken by subjects at any time after (>) the end of the parent study day. Reporting will be done for Cohort A, FAS analysis set.

Disease modifying drugs in CLASSIC

MS-DMDs drugs will be identified using lookup list against all concomitant medication reported as well as eCRF dedicated question. Coding group will provide initial list using drug code, ATC and other elements for the medical team to review and approve prior to data base lock. Final list will be similar to table 3 below and will be standalone document (Appendix 17.2). First, Second, third and any subsequent DMD after first and last dose of Cladribine will also be reported descriptively. Each one will be identified based on the date of the DMD in ascending order since the date of first dose of IMP. First subsequent DMD will be reported by DMD type and ATC and second and third subsequent DMDs will be reported by DMD type only. First subsequent DMD will also be summarized by type, ATC and Medication Name. Patterns of DMD switches will be described also and provided only for the final analysis. Reporting will be done for all cohort, FAS analysis set.
A listing of subsequent DMDs after last IMP dose will be provided for subjects with repeating DMD types.

Table 4: List of MS-DMD

Drug Name	ATCs	SDGs (Standard Drug Groupings)
Alemtuzumab (Campath, MabCampath, Lemtrada)	L01XC, Monoclonal antibodies L04AA, Selective immunosuppressants	Antineoplastic immunosuppressants Monoclonal antibodies - antineoplastics Selective immunosuppressants
Daclizumab (Zinbryta)	L04AC, Interleukin inhibitors	Interleukin inhibitors Monoclonal antibodies - non antineoplastics
Dimethyl fumarate (Tecfidera)	L04AX, Other immunosuppressants	Other immunosuppressants
Fingolimod (Gilenya)	L04AA, Selective immunosuppressants	Selective immunosuppressants
Glatiramer acetate (Copaxone)	L03AX, Other immunostimulants	Other immunosuppressants
interferon beta (Avonex, Rebif, Betaferon, Extavia, Plegridy)	L03AB, Interferons S01AD, Antivirals	Interferons Other antivirals
Laquinimod (Nerventra)	L04AX, Other immunosuppressants N07XX, Other nervous system drugs	Other immunosuppressants

Drug Name	ATCs	SDGs (Standard Drug Groupings)
Mitoxantrone (Novantrone)	L01DB, Anthracyclines and related substances	Antineoplastic anthracyclines and related substances BCRP inhibitors BCRP substrates
Natalizumab (Tysabri)	L04AA, Selective immunosuppressants	Biologic DMARDs Monoclonal antibodies - non antineoplastics Selective immunosuppressants
Ocrelizumab (Ocrevus)	L04AA, Selective immunosuppressants	Biologic DMARDs Monoclonal antibodies - non antineoplastics Selective immunosuppressants
Rituximab (Rituxan)	L01XC, Monoclonal antibodies	Antineoplastic CD20 antigen inhibitors Biologic DMARDs Monoclonal antibodies - antineoplastics
Siponimod	L04AA, Selective immunosuppressants	Selective immunosuppressants
Teriflunomide (Aubagio)	L04AA, Selective immunosuppressants	BCRP substrates Moderate CYP2C8 inhibitors Non-biologic DMARDs OATP1B1 inhibitors Selective immunosuppressants
Hematopoietic stem cell transplant	B05AX, Other blood products	Other blood products
Off-label immunosuppressants (azathioprine, mycophenolate, cyclophosphamide)	L04AX, Other immunosuppressants - azathioprine L04AA, Selective immunosuppressants - mycophenolate L01AA, Nitrogen mustard analogues - cyclophosphamide	Other immunosuppressants - azathioprine Selective immunosuppressants - mycophenolate Non-biologic DMARDs - cyclophosphamide
FINGOLIMOD HYDROCHLORIDE	L04AA, Selective immunosuppressants	Selective immunosuppressants
FUMARIC ACID	D05AX, Other antipsoriatics for topical use D05BX, Other antipsoriatics for systemic use L04AX, Other immunosuppressants V91, Homeopathic preparation	Other immunosuppressants
INTERFERON BETA-1B Betaferon, Extavia???	L03AB, Interferons	Interferons
MITOXANTRONE HYDROCHLORIDE	L01DB, Anthracyclines and related substances	Antineoplastic anthracyclines and related substances BCRP inhibitors BCRP substrates
PEGINTERFERON BETA-1A	L03AB, Interferons	Interferons

13 Study Treatment: Compliance and Exposure

Not Applicable.

14 Efficacy Analyses

No formal statistical hypothesis will be tested, as the study is designed to be exploratory. All analyses will be performed by parent study treatment group and for cohort A except when otherwise specified. In case of low number of participants within a subgroup category as described in section 8.2.2, the subgroup analysis will not be performed for the corresponding efficacy analysis.

14.1 Primary Endpoint

The primary efficacy endpoint of this study will be evaluated descriptively by percentage and 95% CI of patients using a wheelchair most of the time (EDSS ≥7) in the 3 months prior to Study Visit 1 or patients bedridden any time prior to visit 1. Forest plots will also be used to display these results.
In addition, analysis will be adjusted via logistic regression with parent studies (CLARITY or ORACLE), treatment group, and disease duration (at study visit 1) as continuous variable as factors for cohort A and with only disease duration (at study visit 1) as factors for cohort B, C and D. Estimate with likelihood based 95% CI within each parent study treatment group (exposed/not exposed) will be presented.

To identify the primary endpoint, the following source data used will be:

- Both AWB eCRF page and retro EDSS page will be considered. (EDSS >=7 in the 3 month prior to SV1 or EDSS >=8 after FDIMP)
- EDSS>=7 will also be considered (EDSS SV1).
- Participants who died due to MS are included in this proportion also (reason of death is MS disease related).

Disease duration = (SV1 – date of MS diagnosis + 1) / 365.25

Date of MS diagnosis is taken from CLARITY eCRF for CLARITY and CLARITY EXTENSION patients. For ORACLE MS patient, the MS diagnosis is the date of CDMS conversion collected either during the parent study or after the end of the parent study until SV1.

Logistic Regression:

The following SAS code will be used:

```
proc genmod data=sourcedata;
where avalc ne "U";
class STUDY TRT ;
model avalc = STUDY TRT DISEASE_DUR /dist=binomial link=logit lrci wald;
  Estimate "Never Exposed to Cladribine" intercept 1 Trt 1 0    / exp e;
  Estimate "Exposed to Cladribine" intercept 1 Trt 0 1    / exp e;
  Estimate "Never Exposed to Cladribine vs Exposed to Cladribine" Trt -1 1
/exp e;
  lsmeans trt / cl;
  ods output estimates=ESTIMATES lsmeans=lsm; run;
```

14.2 Secondary Endpoint

14.2.1 Long-term disability status

The secondary efficacy endpoint of this study will be evaluated descriptively by percentage and 95% CI of patients with EDSS of 6.0 or higher since last dose of IMP until Visit 1. The results of the confidence scale of EDSS values will be presented descriptively for worst EDSS score (available only for Retro EDSS). The worst EDSS value will be summarized by categories for each cohort.

EDSS will be assessed clinically (on site) and by phone.

14.2.2 Clinical characteristics

The clinical characteristics of study participants will be evaluated descriptively by the subgroups long-term responders and non-responders for Cohort A as per section 9.5. Clinical and demographic characteristics include gender, age, race, ethnicity, region, EDSS Score, number of relapses during last year before enrollment of parent study, prior use of DMDs, HDA Status, education, employment status, time since last IMP (years), type of first DMD after last dose of IMP, disease duration, and disease classification.

14.2.3 MRI characteristics

The MRI characteristics of study participants in the MRI sub-study analysis will be evaluated descriptively at Study Visit 2 by the subgroups of long-term responders and non-responders for all Cohorts as per section 9.5.

The MRI characteristics of study participants in the MRI sub-study analysis include the following MRI variables:

- Number of total T2-W Lesions at Study Visit 2
- Number of total T1-W Lesions at Study Visit 2

- Volume of total T2-W Lesions (cm^3) at Study Visit 2
- Volume of total T1-W Lesions (cm^3) at Study Visit 2
- Brain Volume (cm^3) at Study Visit 2

14.3 Tertiary Endpoint

14.3.1 Real-world treatment patterns

Tertiary endpoints collected retrospectively or at Study Visit 1 will be analyzed descriptively as defined in Section 8. Time, type, and reason for first sequential treatment after first course of IMP, type of second sequential treatment, as well as the frequency of routine clinical monitoring and disease activity status. The "physician sequential treatment decision questions" eCRF page will be used to analyzed first and second sequential treatment (by DMD type only). The "frequency stable patient monitoring questions" eCRF page will be used for the frequency of routine clinical monitoring.

14.3.2 Durability of clinical outcomes

Durability of clinical outcomes will be summarized descriptively and evaluated via retrospective data collection from medical records or at Study Visit 1:

- Proportion of study participants being bedridden
- Time from first dose of IMP to first use of an ambulatory device
- Time from last dose of IMP to first use of an ambulatory device
- Time from first dose of IMP to first use of a wheelchair
- Time from last dose of IMP to first use of a wheelchair
- Number of MS relapses between the end of parent study to Study Visit 1
- ARR from time of first dose of IMP to SV1, and by 2-year intervals
- ARR from time of last dose of IMP to SV1, and by 2-year intervals
- % and Time to conversion to CDMS (For Cohort D participants only)
- Proportion of study participants diagnosed as Secondary Progressive MS (SPMS) without relapses in the 3 months prior to SPMS diagnosis
- Proportion of study participants diagnosed as SPMS with relapses in the 3 months prior to SPMS diagnosis
- Proportion of study participants diagnosed as Primary Progressive MS (PPMS) (For Cohort D participants only)

Computational rule:

Participants being bedridden, first use of an ambulatory device and first use of a wheelchair are collected on "ambulatory - bedridden status and first use of wheelchair" eCRF page.

Participants diagnosed as SPMS with and without relapses in the 3 months prior to SPMS diagnosis are collected on "History of MS onset" eCRF page and Participants diagnosed as PPMS are collected on "conversion to CDMS" eCRF page.

Time to first ambulatory device/wheelchair

Kaplan Meier curve and estimates including number of subjects at risk, number of subjects with an event and subject censored will be presented for time to first ambulatory and wheelchair from first and last dose of IMP administered, by treatment group (exposed vs never exposed) and overall

Computation rule:

Whichever come first will be considered as an event:

1) CRF Ambulatory device page, wheelchair use date
2) CRF Ambulatory device page, ambulatory device use date
3) EDSS score >= 6
4) Death due to MS

Kaplan Meier SAS code:

AVAL = time-to-event response variable
CENSOR = censoring variable (0 = event, 1 = no event)
TRT= Trt group ("Exposed to Clad" "Never exposed to Clad")

Code:

```
PROC LIFETEST DATA=ADTTE OUTSURV=RESULTS ALPHA=0.05 METHOD= KM Conftype =
Loglog;
TIME AVAL*CENSOR(1);
STRATA TRT;
RUN;
```

Annualized Relapse Rate:

ARR from time of FDIMP to Study Visit 1 is calculated for each treatment group:

ARR = [(sum of relapses *365.25) / (sum of time on study in days until SV1)]

ARR from time of FDIMP to Study Visit 1 and by 2-year intervals is calculated for each treatment group:

ARR = [(sum of relapses *365.25) / (sum of time on main study by 2-year intervals in days until SV1)]

Time on study = Study Visit 1 – first dose of IMP +1

ARR from time of last dose of IMP to Study Visit 1 will be calculated similarly.

Table 5: Time window for ARR by 2-year intervals

Cumulative intervals	**Time intervals**
Less than 2 years	1 to 730 days
2nd years to 4th years	731 to 1461 days
4th years to 6th years	1462 to 2191 days
6th years to 8th years	2192 to 2922 days
Xth years to Yth years…	Truncate (X*365.25 +1) to truncate (Y*365.25) days

Time to CDMS (Cohort D only)

Number of participants who converted to CDMS since first and last dose administered will be summarized descriptively.

Both information collected in "Conversion to CDMS" eCRF page and ORACLE MS parent study dataset will be used to identify participants who converted to CDMS after first/last dose of IMP.

14.3.3 Quality of Life and cognitive outcomes

EQ-5D-3L:

The EQ-5D-3L consists of two components - the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises the following five dimensions:

- Mobility
- self-care
- usual activities
- pain/discomfort
- anxiety/depression

Each dimension has three levels: no problems, some problems, extreme problems (labelled 1–3). The respondent is asked to indicate his health state by checking the box against the most appropriate statement in each of the five dimensions. The EQ-5D descriptive system will be summarized for each dimension as continuous variable at study visit 1.

Respondents indicate their self-rated health on the EQ VAS, numbered from 0 to 100 where the endpoints are labelled “Best imaginable health state” (100) and “Worst imaginable health state” (0). This information can be used as a quantitative measure of health outcome as judged by the individual respondents and will be summarize descriptively at study visit 1.

EQ-5D descriptive system and EQ VAS change from the latest assessment prior to or on first dose of IMP will also be summarized descriptively. In case of missing date in parent study, visit labels (e.g., Screening Visit, Baseline Visit, Unscheduled Baseline Visit) will be used to determine baseline visit.

Computation rule:

If there is no EQ-5D score before or on the first dose of IMP day, then the change will not be calculated.

BVMT-R (Cohort D only):

BVMT-R performance test will be summarized using the following raw scores: “Total recall”, “Delay recall”, “Percent retained (%)” and “Learning Consistency (%)”.

Raw scores at study visit 1 and change from ORACLE MS study latest assessment prior to or on first dose of IMP will be summarized descriptively.

Computation rule:

If there is no BVMT-R score before or on the first dose of IMP day, then the change will not be calculated.

SDMT (Cohort D only):

Total SDMT score (i.e. oral score from sdmt eCRF page) at study visit 1 and change from latest assessment prior to or on first dose of IMP will be summarized descriptively.

Computation rule:

If there is no SDMT score before or on the first dose of IMP day, then the change will not be calculated.

14.3.4 Durability of outcomes on brain imaging

Changes in MRI assessment from the last clinical visit in the parent studies (called “Screening”) to Study Visit 2 will be analyzed descriptively for the MRISS analysis population for the following MRI parameters.

- Changes in number of total T2-W Lesions from Screening to Study Visit 2 (only for ORACLE MS)
- Changes in number of total T1-W Lesions from Screening to Study Visit 2
- Percentage changes in volume of total T2-W Lesions from Screening to Study Visit 2 (only for

ORACLE MS)

- Percentage changes in volume of total T1-W Lesions from Screening to Study Visit 2
- Percentage in Brain Volume changes from Screening to Study Visit 2
- Percentage of ventricular Atrophy: Longitudinal from Screening to Study Visit 2

14.3.5 HDA and long-term responders

Responder rates will be analyzed in HDA patients versus the responder rate in non-HDA patients from the Cohort B population and summarized descriptively for the FAS population.

14.3.6 Genetic variations

Optional blood samples for pharmacogenetics testing will be collected at Study Visit 1.
The current plan for PGx is to identify ~20 Single Nucleotide Polymorphism (SNPs) that will be analyzed and validated prior to using in the PGx analysis. Identification of SNP is the responsibility of Clinical Biomarkers and Companion Diagnostics group (CBD) and will be documented in separate document (Appendix 17.4). The PGx analysis will be done approximately 2 years after study completion. The result may be presented on a separate CSR as an addendum to the CSR. The main approach will be to analyze SNP or combination of SNPs subgroup variables with 2-3 categories on primary and secondary endpoints. The rules about analyzing data with small cells or zero cells will be similar to other subgroup analysis. The subgroup analysis for a variable will not be done if we have less than 25% of participant by at least 1 subgroup category in that variable.

Genetic variations will be analyzed descriptively for the primary and secondary endpoints on PGx population based on cohort A. In addition, association of genetic variations with patients experiencing long- term response will be analyzed. Correlations with clinical/imaging endpoints and other data will be explored.

15 Safety Analyses

The subsections in this section include specifications for summarizing safety assessments: adverse events, laboratory tests and vital signs.

15.1 Adverse Events

15.1.1 All Adverse Events

AEs include all AEs which start on or after the CLASSIC ICF signature and will be displayed in listings. All CRF data will be included in the listings, including start and end date, seriousness, severity, Adverse Drug reaction (ADR) will be listed.

All AEs will be summarized using the latest version of MedDRA preferred term (PT) and

MedDRA primary system organ class (SOC) body term as Body System category.

No imputation will be done on listings.

All listings will be grouped by treatment groups for cohort A, FAS analysis set.

15.1.2 Adverse Events Leading to Discontinuation of Study Treatment

Not Applicable

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

15.2.1 Deaths

AEs leading to death will be reported in a listing.

15.2.2 Serious Adverse Events

Serious AEs will be reported in a listing.

15.2.3 Other Significant Adverse Events

Three AEs of special interest (AESIs) will be listed:

- Severe (≥ Grade 3) lymphopenia
- Infections/ opportunistic infections
- Malignancies

AESI will be identified using the "adverse drug reactions related to cladribine or placebo since the end of parent studies details" eCRF page. Only AESI collected via eCRF will be reported in a listing.

15.3 Clinical Laboratory Evaluation

Pregnancy test collected on the eCRF will be listed in dedicated listings.

15.4 Vital Signs

Vital sign summaries will include all vital sign assessments collected at Study visit 1 in the CRF (systolic and diastolic blood pressure (mmHg), pulse rate (BPM) and body temperature (C)]. All vital sign assessments will be listed only.

15.5 Other Safety or Tolerability Evaluations

Not Applicable.

16 References

1. Clinical Study Report. EMR700568-012 Prospective observational long-term safety registry of Multiple Sclerosis patients who have participated in cladribine clinical trials (PREMIERE). Merck Serono SA – Geneva, An affiliate of Merck KGaA, Darmstadt, Germany, 29 quai des Bergues, 1201 Geneva / Switzerland. February 5 2018
2. Clopper, C.J., and Pearson, E.S. The Use of Confidence or Fiducial Limits Illustrated in the Case of the Binomial", (1934)," *Biometrika* 26, 404–41
3. Jiming Fang Institute for Clinical Evaluative Sciences, Canada, 2011, Using SAS® Procedures FREQ, GENMOD, LOGISTIC, and PHREG to Estimate Adjusted Relative Risks – A Case Study, *Statistics and Data analysis, SAS Global Forum* 2011.

17 Appendices

17.1 Table: List of outputs for the interim and final analyses

Outputs	Title	Interim Analysis	Type (Unique, Repeated)
15.1 Demographic and Baseline Data			
15.1.1 Subject Disposition			
Table 15.1.1.1	Subject Disposition – FAS analysis set	Y	U
Table 15.1.1.2	Analysis Sets	Y	U
15.1.2 Important Protocol Deviations			
Table 15.1.2.1	Important Protocol Deviations- FAS analysis set		U
15.1.4 Demographic and Baseline Characteristics			
Table 15.1.4.1	Demographics and baseline characteristics- Cohort A- FAS analysis set	Y	U
Table 15.1.4.2	Demographics and baseline characteristics- Cohort B- FAS analysis set	Y	
Table 15.1.4.3	Demographics and baseline characteristics- Cohort C- FAS analysis set	Y	
Table 15.1.4.4	Demographics and baseline characteristics- Cohort D- FAS analysis set	Y	
Table 15.1.4.5	Distribution by Region and Country - FAS analysis set		U
15.1.5: Medical history			
Table 15.1.5.1	Medical History- Cohort A- FAS analysis set	Y	U
Table 15.1.5.2	Medical History- Cohort B- FAS analysis set		
Table 15.1.5.3	Medical History- Cohort C- FAS analysis set		
Table 15.1.5.4	Medical History- Cohort D- FAS analysis set		
15.1.7: Previous and concomitant Medications, Procedures, Follow-up			
Table 15.1.7.1	Prior and Concomitant Medications in CLASSIC - Cohort A- FAS analysis set		U

Table 15.1.7.2	Disease Modifying Drug for MS subsequent to IMP treatment in Parent study by Type/ATC - FAS analysis set	Y	U
Table 15.1.7.3	Disease Modifying Drug for MS subsequent to IMP treatment in Parent Study by Type/ATC - Cohort A- FAS analysis set	Y	
Table 15.1.7.4	Disease Modifying Drug for MS subsequent to IMP treatment in Parent Study by Type/ATC - Cohort B- FAS analysis set	Y	
Table 15.1.7.5	Disease Modifying Drug for MS subsequent to IMP treatment in Parent Study by Type/ATC - Cohort C - FAS analysis set	Y	
Table 15.1.7.6	Disease Modifying Drug for MS subsequent to IMP treatment in Parent Study by Type/ATC - Cohort D - FAS analysis set	Y	
Table 15.1.7.7	Pattern of Disease Modifying Drug Types for MS subsequent to Cladribine treatment after First Dose of IMP - Cohort A - FAS analysis set	Y	U
Table 15.1.7.8	Pattern of Disease Modifying Drug Types for MS subsequent to Cladribine treatment after First Dose of IMP - Cohort B - FAS analysis set	Y	
Table 15.1.7.9	Pattern of Disease Modifying Drug Types for MS subsequent to Cladribine treatment after First Dose of IMP - Cohort C - FAS analysis set	Y	
Table 15.1.7.10	Pattern of Disease Modifying Drug Types for MS subsequent to Cladribine treatment after First Dose of IMP - Cohort D - FAS analysis set	Y	
Table 15.1.7.11	Pattern of Disease Modifying Drug Types for MS subsequent to Cladribine treatment after Last Dose of IMP - Cohort A - FAS analysis set	Y	
Table 15.1.7.12	Pattern of Disease Modifying Drug Types for MS subsequent to Cladribine treatment after Last Dose of IMP - Cohort B - FAS analysis set	Y	
Table 15.1.7.13	Pattern of Disease Modifying Drug Types for MS subsequent to Cladribine treatment after Last Dose of IMP - Cohort C - FAS analysis set	Y	
Table 15.1.7.14	Pattern of Disease Modifying Drug Types for MS subsequent to Cladribine treatment after Last Dose of IMP - Cohort D - FAS analysis set	Y	
Table 15.1.7.15	Disease Modifying Drug for MS Subsequent to Cladribine Treatment by Type/ATC/Medication Name - FAS Analysis Set	Y	
15.2: Efficacy Data			
15.2.1: Primary Endpoint			

Table 15.2.1.1.1	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden- Cohort A- FAS analysis set	Y	U
Table 15.2.1.1.2	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort A- FAS analysis set- Subset Long-term Responder		
Table 15.2.1.1.3	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort A- FAS analysis set- subset Types of Subsequent DMDs		
Table 15.2.1.1.4	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort A- FAS analysis set- Subset Long-term Responder (Sensitivity Def B)		
Table 15.2.1.1.5	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort A- FAS analysis set- Subset Long-term Responder (Sensitivity Def C)		
Table 15.2.1.2.1	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort B- FAS analysis set		
Table 15.2.1.2.2	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort B- FAS analysis set- Subgroup Treatment course		
Table 15.2.1.2.3	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort B- FAS analysis set- Subset Long-term Responder		
Table 15.2.1.2.4	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort B- FAS analysis set- subset Types of Subsequent DMDs		
Table 15.2.1.2.5	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort B- FAS analysis set- Subgroup Prior Use of DMD		
Table 15.2.1.2.6	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort B- FAS analysis set- Subgroup HDA		
Table 15.2.1.2.7	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort B- FAS analysis set- Subset Long-term Responder (Sensitivity Def B)		
Table 15.2.1.2.8	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort B- FAS analysis set- Subset Long-term Responder		

	(Sensitivity Def C)		
Table 15.2.1.3.1	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort C- FAS analysis set		
Table 15.2.1.3.2	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort C- FAS analysis set- Subset Long-term Responder		
Table 15.2.1.3.3	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort C- FAS analysis set- Subset Types of Subsequent DMDs		
Table 15.2.1.3.4	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort C- FAS analysis set- Subset Long-term Responder (Sensitivity Def B)		
Table 15.2.1.3.5	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort C- FAS analysis set- Subset Long-term Responder (Sensitivity Def C)		
Table 15.2.1.4.1	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort D- FAS analysis set		
Table 15.2.1.4.2	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort D- FAS analysis set- Subset Long-term Responder		
Table 15.2.1.4.3	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort D- FAS analysis set- Subset Types of Subsequent DMDs		
Table 15.2.1.4.4	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort D- FAS analysis set- Subset Long-term Responder (Sensitivity Def B)		
Table 15.2.1.4.5	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort D- FAS analysis set- Subset Long-term Responder (Sensitivity Def C)		
Figure 15.2.1.1.1	Forest Plot of Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden- Cohort A- FAS analysis set		
15.2.2: Secondary Endpoint 1			

Table 15.2.2.1.1	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP – Cohort A- FAS analysis set	Y	U
Table 15.2.2.1.2	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort A- FAS analysis set- Subset Long-term Responder		
Table 15.2.2.1.3	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort A- FAS analysis set- Subset Types of Subsequent DMDs		
Table 15.2.2.1.4	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort A- FAS analysis set- Subset Long-term Responder (Sensitivity Def B)		
Table 15.2.2.1.5	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort A- FAS analysis set- Subset Long-term Responder (Sensitivity Def C)		
Table 15.2.2.2.1	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP – Cohort B- FAS analysis set		
Table 15.2.2.2.2	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP – Cohort B- FAS analysis set- Subgroup Treatment Course		
Table 15.2.2.2.3	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP – Cohort B- FAS analysis set- Subset Long-term Responder		
Table 15.2.2.2.4	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP – Cohort B- FAS analysis set- Subset Types of Subsequent DMDs		
Table 15.2.2.2.5	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP – Cohort B- FAS analysis set- Subgroup Prior Use of DMDs		
Table 15.2.2.2.6	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP – Cohort B- FAS analysis set- Subgroup HDA		
Table 15.2.2.2.7	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort B- FAS analysis set- Subset Long-term Responder (Sensitivity Def B)		
Table 15.2.2.2.8	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort B- FAS analysis set- Subset Long-term Responder (Sensitivity Def C)		
Table 15.2.2.3.1	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP –Cohort C- FAS analysis set		
Table 15.2.2.3.2	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP –Cohort C- FAS analysis set- Subset Long-term Responder		

Table 15.2.2.3.3	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP –Cohort C- FAS analysis set- Subset Types of Subsequent DMDs		
Table 15.2.2.3.4	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort C- FAS analysis set- Subset Long-term Responder (Sensitivity Def B)		
Table 15.2.2.3.5	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort C- FAS analysis set- Subset Long-term Responder (Sensitivity Def C)		
Table 15.2.2.4.1	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP –Cohort D- FAS analysis set		
Table 15.2.2.4.2	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP –Cohort D- FAS analysis set- Subset Long-term Responders		
Table 15.2.2.4.3	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP –Cohort D- FAS analysis set- Subset Types of Subsequent DMDs		
Table 15.2.2.4.4	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort D- FAS analysis set- Subset Long-term Responder (Sensitivity Def B)		
Table 15.2.2.4.5	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP– Cohort D- FAS analysis set- Subset Long-term Responder (Sensitivity Def C)		
Table 15.2.2.5.1	Worse EDSS since last dose of IMP – Cohort A – FAS analysis set	Y	U
15.2.3: Secondary Endpoint 2			
Table 15.2.3.1.1	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort A -FAS analysis set	Y	U
Table 15.2.3.1.2	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort A -FAS analysis set (Sensitivity Def B)		
Table 15.2.3.1.3	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort A -FAS analysis set (Sensitivity Def C)		
Table 15.2.3.2.1	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders – Cohort B -FAS analysis set		
Table 15.2.3.2.2	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort B -FAS analysis set (Sensitivity Def B)		
Table 15.2.3.2.3	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort B -FAS analysis set (Sensitivity Def C)		

Table 15.2.3.3.1	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders – Cohort C -FAS analysis set		
Table 15.2.3.3.2	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort C -FAS analysis set (Sensitivity Def B)		
Table 15.2.3.3.3	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort C -FAS analysis set (Sensitivity Def C)		
Table 15.2.3.4.1	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders – Cohort D -FAS analysis set		
Table 15.2.3.4.2	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort D -FAS analysis set (Sensitivity Def B)		
Table 15.2.3.4.3	Clinical characteristics at Study Visit 1 of long-term responders vs non-responders –Cohort D -FAS analysis set (Sensitivity Def C)		
15.2.4: Secondary Endpoint 3			
Table 15.2.4.1.1	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort A – MRISS analysis set		U
Table 15.2.4.1.2	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort A – MRISS analysis set (Sensitivity Def B)		
Table 15.2.4.1.3	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort A – MRISS analysis set (Sensitivity Def C)		
Table 15.2.4.2.1	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort B – MRISS analysis set		
Table 15.2.4.2.2	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort B – MRISS analysis set (Sensitivity Def B)		
Table 15.2.4.2.3	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort B – MRISS analysis set (Sensitivity Def C)		
Table 15.2.4.3.1	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort C- MRISS analysis set		
Table 15.2.4.3.2	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort C – MRISS analysis set (Sensitivity Def B)		
Table 15.2.4.3.3	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort C – MRISS analysis set (Sensitivity Def C)		
Table 15.2.4.4.1	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort D- MRISS analysis set		
Table 15.2.4.4.2	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort D – MRISS analysis set (Sensitivity Def B)		
Table 15.2.4.4.3	MRI characteristics at Study Visit 2 of long-term responders vs non-responders – Cohort D – MRISS analysis set (Sensitivity Def C)		

15.2.5: Tertiary Endpoint 1			
Table 15.2.5.1	Real-world treatment patterns in study participants – Cohort A- FAS analysis set		U
15.2.6: Tertiary Endpoint 2			
Table 15.2.6.1	Durability of clinical outcome– Cohort A – FAS analysis set		U
Table 15.2.6.2	Kaplan Meier- Time to first ambulatory device/wheelchair - Cohort A -FAS analysis set	Y	U
Figure 15.2.6.1	Kaplan Meier- Time to first ambulatory device/wheelchair by Exposed/Never Exposed Group - Cohort A -FAS analysis set	Y	U
Figure 15.2.6.2	Kaplan Meier - Time to First Ambulatory Device/Wheelchair - Cohort A - FAS Analysis Set	Y	
15.2.7: Tertiary Endpoint 3			
Table 15.2.7.1	Change in Quality of life outcomes – Cohort A- FAS analysis set	Y	U
Table 15.2.7.2	Change in Cognition outcomes (BVMT-R score)– Cohort D- FAS analysis set		U
Table 15.2.7.3	Change in Cognition outcomes (SDMT score) – Cohort D- FAS analysis set		U
15.2.8: Tertiary Endpoint 4			
Table 15.2.8.1	Change in MRI assessment from Baseline to Study Visit 2– Cohort A -MRISS analysis set		U
15.2.9: Tertiary Endpoint 5			
Table 15.2.9.1	Responder rate by HDA/Non-HDA patients – Cohort B-FAS analysis set		U
15.2.10: Additional analysis			
Table 15.2.10.1	Additional analysis: Comparison between baseline characteristics from Non-CLASSIC/CLASSIC patients- WPS analysis set		U
15.2.11: PGX Analysis (tables will be repeated for each SNP or combination of SNPs.)			
Table 15.2.11.1.1	Proportion of patients using a wheelchair (EDSS>=7) the majority of the time in the 3 months prior to Study Visit 1 or bedridden – Cohort A – Subgroup with Presence of SNP1 gene - PGX Population		
Table 15.2.11.2.1	Proportion of patients with EDSS of 6.0 or higher since last dose of IMP – Cohort A – Subgroup with Presence of SNP1 gene - PGX Population		

Table 15.2.11.3.1	Clinical characteristics at Study Visit 1 of long-term responders vs Non-Responders – Cohort A– Subgroup with Presence of SNP1 gene - PGX Population		
Table 15.2.11.4.1	MRI characteristics at Study Visit 2 of long-term responders vs Non-Responders – Cohort A – Subgroup with Presence of SNP1 gene – PGX/MRISS Population		
16.2.2 Protocol Deviations Listings			
Listing 16.2.2.1	Listing of Important Protocol Deviations – Cohort A		U
16.2.3: Medical History			
Listing 16.2.3.1	Listing of Medical History – Cohort A		U
16.2.4: Previous and Concomitant Medications			
Listing 16.2.4.1	Previous and Concomitant Medications – Cohort A		U
Listing 16.2.4.2	Subsequent Disease Modifying Drugs (DMDs) after Last IMP Dose for Subjects with Repeating DMD Types - Cohort A - FAS Analysis Set	Y	U
16.2.7 Adverse Event Listings			
Listing 16.2.7.1	All Adverse Events - Cohort A		U
Listing 16.2.7.2	All Serious Adverse Event - Cohort A		U
Listing 16.2.7.3	All Adverse Events leading to death - Cohort A		U
Listing 16.2.7.4	All Adverse Events of Special Interest - Cohort A		U
16.2.8 Laboratory Values Listings			
Listing 16.2.8.1	Pregnancy - Cohort A		U
Listing 16.2.8.2	Vital Signs – Cohort A		U

17.2 DMD List (standalone document)

17.3 Clinically Important Protocol Deviations (standalone document)

17.4 Pharmacogenetics parameters (standalone document)