Integrated Analysis Plan

Study Number:	MS700568-0150
Clinical Study Protocol Title:	Cladribine tablets in Highly-active Relapsing Multiple Sclerosis - Real-World Effectiveness in UK Clinical Practice (CAMELOT-MS)
Study Phase:	Phase IV
Merck Compound:	Cladribine tablets
Protocol Version:	25 March 2022/Version 2.0
Integrated Analysis Plan Author:	**Coordinating Author** PPD PPD **Function** / **Author(s)** PPD
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Approval Page

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Cladribine tablets in Highly-**a**ctive Relapsing **M**ultiple Sclerosis - R**ea**l-W**o**rld Effec**t**iveness in UK Clinical Practice (CAMELOT-MS)

PPD

1 Table of Contents

2 List of Abbreviations and Definition of Terms

AE – Adverse event

ARR – Annualised relapse rate

CI – Confidence interval

CRF – Case report form

CSR – Clinical study report

eCRF – (electronic) Case Report Form

DMT – Drug modifying therapy

EDSS – Expanded disability status scale

ENR – Enrolled Analysis Set

FAS – Full Analysis Set

IAP – Integrated Analysis Plan

IPD – Important protocol deviations

KM – Kaplan-Meier

MedDRA – Medical Dictionary for Regulatory Activities

PT – Preferred Term

RFR – relapse-free rate

SCR – Screening analysis set

SD – Standard deviation

SOC – System Organ Class

TEAE – Treatment-Emergent Adverse Event

TEAESI – TEAE of Special Interest

TFL – Time to first lesion

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	17SEP2021	PPD	First version
2.0	15DEC2022		Removal of references to the interim analysis Revision of medical history and comorbidities definitions Revision of previous therapies and procedures definition
3.0	12SEP2023		Inclusion of additional courses of cladribine treatment after Year 2 Revision of imputation rules for partial dates Addition of chart review 2 timing to patient disposition Updated section 15.2 to add grades of lymphocyte counts Updated section 14.2.2 for definition of treatment discontinuation

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated analysis plan (IAP) is to document technical and detailed specifications for the analysis of data collected for protocol MS700568-0150. Results of the analyses described in this IAP will be included in the final clinical study report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 9.7 (Data Analysis) of the study protocol and protocol amendments and is prepared in compliance with ICH E9. It describes analyses planned in the protocol and protocol amendments.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	IAP section
Primary		
To analyse the annualised relapse rate (ARR) yearly up to 5 years after cladribine tablet initiation.	**Effectiveness:** - ARR at 1, 2, 3, 4, 5 years after cladribine initiation.	14.1.1
Secondary		
To analyse the proportion of relapse-free patients at each year (and up to 5 years) after cladribine tablet initiation.	**Effectiveness:** - Number and % of relapse-free patients at 1, 2, 3, 4, 5 years after cladribine initiation.	14.2.1
To analyse the time after cladribine tablet initiation to first relapse.	**Effectiveness:** - Time to first relapse from cladribine initiation.	14.2.1

Objectives	Endpoints (Outcome Measures)	IAP section
To evaluate the proportion of patients who discontinued cladribine tablets and reasons for discontinuation.	**Effectiveness:** - Number and % of patients who discontinued cladribine. - Number and % of reasons for discontinuation.	14.2.2
To evaluate the subsequent disease modifying therapies (DMTs) received after cladribine tablets discontinuation up to 5 years after cladribine tablets initiation.	**Effectiveness:** - Number of subsequent DMTs. - Number and % of patients who received subsequent DMTs. - Time to first subsequent DMT from last dose of cladribine. - Time to second subsequent DMT from last dose of cladribine.	14.2.3
To analyse the proportion of patients with disability progression confirmed over 6 months, 2 years after treatment initiation.	**Effectiveness:** - Change from baseline to year 2 in EDSS - Number and % of patients with disability progression confirmed over 6 months.	14.2.4
To analyse the incidence of selected, identified, and potentially clinically important adverse events (AEs).	**Safety:** - Number and % of patients with AEs - Number and % of patients with AEs by preferred term (PT) and system organ class (SoC).	15.1
Others		
To evaluate MS-related lesions as assessed by MRI in patients with HDA-RRMS after cladribine tablet initiation.	**Effectiveness:** - Number and % of patients with: o T1 gadolinium enhancing lesions, o T2 new lesions, o T2 enlarging lesions.	16.1

6 Overview of Planned Analyses

The final analysis will be performed once the study is completed with the purpose of evaluating all outcomes and the database is locked. The final analysis will include data collected during the first and the second chart abstractions. The database will be locked once the second chart abstraction is completed on all patients unless they withdrew consent, discontinued the study, or were lost to follow-up.

7 Changes to the Planned Analyses in the Clinical Study Protocol

There are no changes to the planned analyses in the clinical study protocol.

8 Analysis Sets and Subgroups

8.1 Definition of Analysis Sets

Screening Analysis Set (SCR)

The Screening analysis set (SCR) includes all participants who signed the informed consent.

Enrolled Analysis Set (ENR)

Patients in the SCR who met eligibility criteria.

Full Analysis Set (FAS)

Patients in the Enrolled Analysis Set (ENR) who were treated with at least one course of treatment with cladribine tablets.

8.2 Subgroup Definition and Parameterization

Subgroup analyses will be performed on primary and secondary outcomes. All subgroup analyses will be exploratory, no adjustment for multiplicity will be performed.

The following subgroups will be defined:

Most recent prior disease-modifying therapy:

- Naïve to disease-modifying therapies
- Prior platform therapy
- Prior high-efficacy cell-depleting treatment
- Prior high-efficacy non-depleting treatment

Prior and subsequent disease-modifying therapies will be medically reviewed on an ongoing basis and classified by the medical advisor. This process will be described in a separate document. DMTs classes will be linked with electronic case report form (eCRF) data for data analysis.

9 General Specifications for Data Analyses

Index date

Cladribine initiation date will be used as an index date to determine baseline and on-treatment periods.

Initial date

According to the protocol, data will be collected counting from 1 year prior to cladribine initiation date. The initial date will be calculated as follows:

- Initial date: Index date/cladribine initiation date - 1 (year).

All assessments occurred from initial date onwards will be considered for the analysis.

Pre-treatment period is defined as follows:

- Pre-treatment: from initial date until cladribine initiation date - 1 (day).

Listings

In the individual participant data listing all individual data will be listed as measured. Repeated measurements will be included in the listings. All listings will be sorted by subject ID, study period, and date of assessment as appropriate.

Tables and Descriptive Statistics

All data will be summarised by the most recent prior DMT group and overall. Repeated measurements (in the same time window) included in the listings will not be used for statistical analyses or summaries unless the repeated measurement was performed due to unreliable values/technical reasons.

Unless otherwise specified, continuous variables will be summarised using descriptive statistics, i.e. the number of participants with non-missing values (n), the number of participants with missing values, (nmiss), mean, standard deviation (SD), median, 25th percentile (Q1) and 75th percentile (Q3), minimum, and maximum. If there are no missing values, the number of participants with missing values should be indicated by a 0.

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

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

9.1 Definition of Baseline and Change from Baseline

In general, the last non-missing measurement prior to the index date (i.e. cladribine initiation date) will be used as the baseline measurement for analyses that require change from baseline calculation (e.g. EDSS analysis).

If an assessment is performed on the same day as cladribine initiation it will be assumed that it was performed prior to treatment start and will be considered as baseline. Last non-missing measurements occurred more than 60 days before cladribine initiation will not be considered ‘baseline’.

Changes from baseline are defined as:

Change = visit/year value – baseline value

9.2 Study Day

Day 1 is the day of cladribine initiation date (i.e. index date), the day before is Day -1 (no Day 0 is defined). Study day is defined relative to Day 1.

9.3 Definition of Duration and 'Time Since' Variables

Durations in days will be calculated by the difference of start and stop date + 1 (e.g. duration of diagnosis at cladribine initiation (days) = date of MS diagnosis – date of cladribine initiation + 1) if not otherwise specified.

9.4 Conversion Factors

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

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

9.5 Date of Last Contact

The date of last contact will be derived for participants not known to have died at the analysis cut-off using the latest complete date prior to or at the data cut-off date among the following:

- AE start and end dates
- Cladribine start and end dates
- DMT start and end dates
- Concomitant medications/procedures start and end dates
- Onset of relapse and stabilisation/resolution dates
- EDSS assessment dates
- Lab collection dates
- MRI scan dates

Assessment dates after the cut-off date will not be applied to derive the last contact date. Imputed dates will contribute to the last contact date derivation if the month and year are available and only the missing day is imputed.

9.6 Time Window

For analyses conducted at yearly intervals (e.g. relapse rate at each year) the date of the event will be assigned an analysis time-point according to Table 1:

Table 1. Time windows for relapses analysis

Time-point	Study day	
	From	To
Year -1	-365	-1
Year 1	84*	365
Year 2	366	731
Year 3	732	1096
Year 4	1097	1461
Year 5	1462	1826

*Relapses occurred within the induction period window of 12 weeks (84 days) will not be included in the main analysis. Sensitivity analyses will be repeated changing Year 1 interval to (56 to 365 days) and (1 to 365 days) respectively.

For EDSS analysis on disability progression the Table 2 will be followed:

Table 2. Time window for EDSS analysis

Time-point	First assessment		
	Study day		
	From	Mid-point	To
Baseline	-60	-	1
Year 2 (treatment start date) OR Year 2	183	365	548

The closer assessment to the Year 2 treatment start date will be used. If the patient does not receive any treatment at Year 2, Table 2 time-window will be used to derive the Year 2 EDSS assessment. The confirmatory EDSS score assessment (used to confirm disability progression) will be selected in the (+91; +272) days interval from the 'Year 2' assessment date. In case of multiple assessments within this window the closer to +182 days from the 'Year 2' assessment date will be picked.

In case of multiple assessments at the same distance of the mid-point the earliest one will be considered for the analysis. All measurements will be listed.

9.7 Definition of On-treatment Period

Three different on-treatment periods will be defined based upon the induction period definition as follows:

Table 3. On-treatment periods

On-treatment period	Study day	
	From	To
Full effectiveness	84	Minimum of - Cut-off date - Date of death
Amplified effectiveness	56	
Full treatment	1	

9.8 Exposure time

Duration of exposure = date of last dose of cladribine – date of first dose of cladribine +1.

9.9 Follow-up time

Follow-up period is defined as follows:

- Follow-up: from date of last dose of cladribine until date of last contact (see Section 9.5).

9.10 Imputation of Missing Data

Unless otherwise specified, all data will be evaluated as observed, and no imputation method for missing values will be used. In all participant data listings, imputed values (e.g. partial dates) will be presented, and imputed information will be flagged.

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

The following table for imputation rules for missing/partial dates will be considered:

Disease history	Incomplete dates for MS diagnosis will be imputed as follows: • If the day is missing, it will be imputed to the 15th day of the month. • If both day and month are missing and the year is prior to the year of cladribine initiation, the month and day will be imputed as July 1st. • If both day and month are missing and the year is same as the year of cladribine initiation, the month and day will be imputed as January 1st. • If the date is completely missing, no imputation will be performed.
Relapses	Start day of relapse:

	• If the day is missing and the month and year are available, the day will be imputed to the first day of the month. • If the day and month are missing, the start date will be imputed to the 1st day of the available year. End date of the relapse: • If the relapse is ongoing, the end date will be imputed to the date of last contact. • If the day is missing and the month and year are available, the missing day will be imputed to the last day of the month, if following the start date of relapse. • If both the day and month are missing, the end date will not be imputed.
Adverse events	Incomplete AE-related dates will be imputed as follows: • In case the onset date is partially missing but the onset month and year, or the onset year are equal to cladribine initiation then the onset date will be imputed by the minimum of cladribine initiation date and AE resolution date (if not missing). • In all other cases, the missing onset day or missing onset month will be imputed by 1. • Incomplete stop dates will be imputed by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case, the date of death will be used to impute the incomplete stop date. • In all other cases, the incomplete stop date will not be imputed.
Previous and concomitant medication (including prior/subsequent DMTs)	Incomplete prior/concomitant medication (and DMT) start and stop dates will be imputed as follows: • If the medication start date is missing completely, then the medication start date will be replaced by the cladribine initiation date. • If the day of medication start date is missing, but the month and year are equal to the cladribine initiation date, then the medication start date will be replaced by the cladribine initiation date. For example, if the medication start date is --/JAN/2015, and cladribine initiation date is 15/JAN/2015, then the imputed medication start date will be 15/JAN/2015. • If both the day and month of medication start date are missing but the start year is equal to the cladribine initiation date, then the medication start date will be replaced by the cladribine initiation date. For example, if the medication start date is --/---/2014, and cladribine initiation date is

	19/NOV/2014, then the imputed medication start date will be 19/NOV/2014. • In all other cases the missing medication day or missing medication month will be replaced by 1. Incomplete stop date will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of participant's death. In the latter case the date of death will be used to impute the incomplete stop date. • In all other cases the incomplete medication stop date will not be imputed. In case an imputed medication start date is later than the medication stop date, it will be replaced by the medication stop date.
Dates of cladribine	Start date of cladribine : • If the day is missing and the month and year are available, the missing day will be imputed to the 15th of the month. • If both the month and day are missing and the year is available, and the end date is available for cladribine treatment Year 1 Week 2, cladribine initiation date will be imputed to the first day of the month prior to the date of Year 1 Week 2. For example, if the end date of week 2 is --/FEB/2019, the cladribine initiation date will be 01/JAN/2019. End date of cladribine : • If the last date of cladribine is completely missing and no death date the participant should be considered to be ongoing and use the cut-off date for the analysis as the last dosing date • If the last date of cladribine is partially missing, then imputed last dose date is: = Last day of the month, if both Year and Month are available and Year = Year of min (discontinuation date, death date) and Month < the month of min (discontinuation date, death date)

10 Study Participants

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

10.1 Disposition of Participants and Discontinuations

The following will be presented in a summary table by the most recent prior DMT and overall:

- Total number of participants screened

- Number of screened participants who discontinued from the study after screening will be summarised overall and grouped by the main reason for discontinuation:
    - Participant did not meet all eligibility criteria
    - Withdrew consent
    - Other
- Number of enrolled participants
- Number of patients in the Full analysis set (FAS)
- Number of patients in the FAS who completed study
- Number of patients by timing of the second chart review: The second chart review should be approximately 1 year from enrolment (365 calendar days ± 14 calendar days).
    - Within the protocol-defined window
    - Outside the protocol-defined window
- Number of patients in the FAS who discontinued the study, with the primary reason of discontinuation:
    - AE
    - Death
    - Withdrawal by subject
    - Enrolment in an investigational clinical trial during the study period
    - Other [(COVID-19-related and COVID-19-non-related)]

Listings of discontinued participants will be provided. A listing of participants affected by the COVID-19-related study disruption by unique participant identifier will also be provided.

10.2 Protocol Deviations / Exclusion from Analysis Sets

10.2.1 Important Protocol Deviations

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

Protocol deviations will be collected from sites according to the study Protocol Deviation Plan version 1.0 from 21 July 2021. A frequency table with all protocol deviations based on FAS will be presented.

11 Demographics and Other Baseline Characteristics

Demographics and baseline characteristics will be presented for the FAS by the most recent prior DMT and overall.

11.1 Demographics

Demographic characteristics and physical measurements will be summarised descriptively using the following information from the demographic eCRF page:

- Sex (male, female)
- Age at time of informed consent (years)
- Height (cm, inches, unknown)
- Weight (kg, pounds, unknown)

Specifications for computation:

In case age is not collected in eCRF it will be derived as follows:

- Age (years) = (Informed consent year - year of birth)

In case height is recorded in inches it will be converted in cm as follows:

- Height (cm) = height (inches) x 2.54

In case weight is recorded in pounds it will be converted in kg as follows:

- Weight (kg) = weight (pounds) x 0.453592

11.2 Medical History and Comorbidities

Medical history and comorbidities (past and ongoing) will be presented for the FAS. It will be categorized as follows:

- Past medical history and comorbidities: any disease resolved during the pre-treatment period defined in Section 9 (year prior to cladribine initiation).

- Ongoing comorbidities: any disease that started or is ongoing at cladribine initiation

Any disease that was resolved more than one year prior to cladribine initiation is not relevant will not be included in the analysis.

Medical history and comorbidities will be summarised from the "Medical History and comorbidities" eCRF page, using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version at the time of database lock, preferred term (PT) 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.

12 Previous or Concomitant Therapies/Procedures

Medications will be presented for the FAS by the most recent prior DMT and overall. Previous and concomitant medications will be presented in separate tables and are defined as follows:

- Previous medications are defined as any medication discontinued during the year prior to cladribine initiation.

- Concomitant medications are defined as any medication taken during the course of the study, with a starting date greater than or equal to the administration of cladribine , or with a starting date prior to the administration of cladribine and ongoing at the time of the administration of cladribine .

The World Health Organization Drug dictionary (WHO-DD) will be used for coding of prior and concomitant medications and they will be described using PT as applicable. The most recent version of WHO-DD available at the time of data-cut will be used for medications coding.

Previous and concomitant medications will be listed. Concomitant procedures, if any, will also be listed.

13 Exposure

The following analyses will be performed based on the FAS by the most recent prior DMT and overall.

All calculations and summaries for treatment in Year 1 and Year 2 of cladribine will be based on "Treatment with cladribine Tablets" eCRF page. For additional courses of cladribine (Year 3, Year 4, Year 5 data will be pulled from the "Prior and Subsequent Disease Modifying Therapy" eCRF page if the treatment reported is "cladribine".

The summary of cladribine exposure will include the following information:

- Number of tablets taken per week of 'Year 1','Year 2' and each subsequent course of cladribine
- Total number of tablets taken on 'Year 1', 'Year 2' and each subsequent course of cladribine
- Cumulative number of tablets taken (cumulative over Year 1 and Year 2, and cumulative over all courses of cladribine treatment)
- Number % of patients with no dose and dose delayed (with the corresponding reasons)
- Number % of patients with a complete course of cladribine at 'Year 1', 'Year 2', any additional courses of cladribine treatment and overall

14 Effectiveness

The following analyses will be performed based on the FAS by the most recent prior DMT and overall.

14.1 *Primary Outcome:* ARR

14.1.1 *Primary Objective: Derivation and analysis of the primary outcome:* ARR

The annualised relapse rate (ARR) will be derived from the 'Clinical Confirmed Relapses' CRF page.

The relapses observed will be assigned for the calculation for the ARR as indicated on Table 1 in Section 9.6.

The ARR for a patient will be calculated by dividing the number of clinicians confirmed relapses observed within each period (Year) by the person-years of the patient in the period.

The person-years for a patient will be assigned as follows:

- (365.25-84)/365.25 years for time-point 'Year 1' for the full effectiveness period (main analysis)
- (365.25-56)/365.25 years for time-point 'Year 1' for the amplified effectiveness period (sensitivity analysis #1)
- 1 year for time-point 'Year 1' for the full treatment effectiveness period (sensitivity analysis #2)

And 1 year for each other interval (-1, 2, 3, 4, 5) unless the date of last contact occurs within that interval. In this case that interval person-years will be calculated until the date of last contact. The patient will not contribute to the ARR calculation for the following intervals (if any).

The 95% confidence interval (CI) will be calculated using the exact Poisson method.

14.2 Secondary Outcomes

14.2.1 *Secondary Objective: Derivation and analysis of the secondary outcome:* RFR

The relapse-free rate (RFR) is defined as the time from the on-treatment period start date (see Table 3) until the date of the first relapse or death as assessed by the investigator:

- RFR (years): (First relapse date or death or date of censoring - on-treatment start date + 1) / 365.25.

The main analysis will be based upon the full effectiveness period start date. Sensitivity analyses will be repeated on the amplified and full treatment periods start dates respectively.

Patients who did not have any relapse or have died will be censored at the date of last contact.

The RFR will be summarised using the total number and % of patients with an event and the type of event (relapse, death). The number and % of censored patients will be also presented.

The RFR and associated 95% CI will be summarised at yearly intervals using the Kaplan-Meier (KM) method, the median RFR and corresponding 95% CI (whenever estimable) will be also included. KM curves will be provided.

14.2.2 *Secondary Objective: Derivation and analysis of the secondary outcome:* Treatment discontinuation

A patient will be considered to have discontinued the treatment if he/she does not complete the full treatment course (i.e. 2 weeks in 2 consecutive years). In this case, date of treatment discontinuation will be the date of switch to other DMTs, i.e. the earliest start date of any DMTs following the last date of administration of cladribine. If the patient did not receive any DMTs after the last dose of cladribine, the date of treatment discontinuation will be the last date of administration as recorded in the 'Treatment with Cladribine Tablets' CRF page.

The number and % of patients who discontinued the treatment will be summarised in the disposition table. The number and % of patients who switched to other DMTs will also be reported.

The reason for treatment discontinuation will be derived from the record where the last date of administration is recorded. Reasons will be summarised as follows:

- AE (as per CRF)
- Missed dose (as per CRF)
- Other (as per CRF)

Patients who did not complete the treatment and did not have any of the above reasons reported to their last record will be classified as:

- 'Incomplete course of cladribine treatment'

14.2.3 *Secondary Objective: Derivation and analysis of the secondary outcome:* Subsequent DMTs

DMTs are treatments reported in the "Prior and Subsequent Disease Modifying Therapy" eCRF page excluding cladribine. The number and % of patients with subsequent DMTs will be summarised by preferred names.

The time to first subsequent DMT (T1DMT) is defined as the time from the date of last dose of cladribine until the date of the first subsequent DMT:

- T1DMT (years): (Date of start of first subsequent DMT - last cladribine administration date + 1)/365.25.

Patients who did not start any subsequent DMT will be censored at the date of last contact.

The T1DMT will be summarised using the total number and % of patients with an event. The number and % of censored patients will be also presented.

The T1DMT and associated 95% CI will be summarised at yearly intervals using the KM method, the median TSDMT and corresponding 95% CI (whenever estimable) will be also included. KM curves will be provided.

Time to second subsequent DMT (T2DMT) will be derived as follows:

- T2DMT (years): (Date of start of second subsequent DMT - last cladribine administration date + 1)/365.25.

The T2DMT will be summarised in the same way of T1DMT only if at least 5% of patients have a second subsequent DMT recorded.

14.2.4 *Secondary Objective: Derivation and analysis of the secondary outcome:* EDSS and disability progression

The Annual EDSS results at cladribine initiation and at Year 2 and the corresponding change from baseline (i.e. cladribine initiation) will be summarised using descriptive statistics. Scores will be derived from the 'Annual EDSS scores' CRF page. All other assessment will be presented in a listing.

The number and % of patients with disability progression confirmed over 6 months at Year 2 after cladribine initiation will be also summarised.

EDSS progression is defined as an increase in the EDSS scale as follows:

- If the EDSS score at cladribine tablet initiation is 0, the increase must be ≥1.5 units
- If the EDSS score at cladribine tablet initiation is ≥0.5 or ≤4.5, the increase must be ≥1.0 units
- If the EDSS score at cladribine tablet initiation is ≥5.0, the increase must be ≥0.5 units.

EDSS assessments will be assigned to time windows as defined in Section 9.6.

15 Safety Analyses

Safety analyses will be performed based on the FAS by the most recent prior DMT and overall.

15.1 Adverse Events

The Treatment-Emergent Adverse Event (TEAE) are those events with onset dates occurring within the full treatment period as defined in Section 9.7.

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

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

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

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

15.1.1 All Adverse Events

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

Incomplete AE-related dates will be handled as specified in Section 9.10.

The following tables will be created:

- TEAE summary table with the number and percentage of patients that have:
  - TEAE
  - TEAE of Special Interest (TEAESI)
    - Grade 3 Lymphopenia
    - Grade 4 Lymphopenia
    - Herpes infections
    - Serious/opportunistic infections
    - Malignancies
  - TEAE leading to death

- TEAE leading to cladribine dose reduction
- TEAE leading to cladribine dose increase
- TEAE leading to cladribine temporary interruption
- TEAE leading to cladribine permanent discontinuation
- TEAE not recovered/resolved
- Any serious TEAE:
  - TEAESI
  - Leading to death
  - Leading to cladribine dose reduction
  - Leading to cladribine dose increase
  - Leading to cladribine temporary interruption
  - Leading to cladribine permanent discontinuation
  - Not recovered/resolved
- Cladribine-related TEAE:
  - TEAESI
  - Serious
  - Leading to death
  - Leading to cladribine dose reduction
  - Leading to cladribine dose increase
  - Leading to cladribine temporary interruption
  - Leading to cladribine permanent discontinuation
  - Not recovered/resolved

- The number and percentages of patients with TEAE by Primary SOC and PT
- The number and percentages of patients with TEAESI by Primary SOC and PT
- The number and percentages of patients with serious TEAE by Primary SOC and PT
- The number and percentages of patients with TEAE related to cladribine by Primary SOC and PT

TEAESI will be individuated using standardized and/or customized MedDRA queries that will be shared by Merck safety department using the dictionary version available at the time of the final analysis data-cut.

15.2 Clinical Laboratory Evaluation

Baseline Lymphocytes results and highest and lowest change from baseline (cladribine initiation) will be summarised. Only the most extreme (lowest and highest) post-baseline Lymphocytes assessments will be retained in the analysis and used for the lowest and highest change from baseline analyses respectively. In case only one post-baseline result is available, it will be used for both analyses.

Lymphocytes results will be summarised descriptively and change from baseline will be calculated if available. In addition, lymphocytes counts will be classified by grade as follows (Fisher et al., 2017):

- Normal lymphocyte level: ≥1.0 10^9/L (lower level of normal)
- Grade 1: 0.8 to <1.0 10^9/L
- Grade 2: 0.5 to <0.8 10^9/L
- Grade 3: 0.2 to <0.5 10^9/L
- Grade 4: <0.2 10^9/L

Lymphocytes will be displayed in 10^9/L unit.

Results reported in other units will be converted as follow:

10^9/L = Cells/mm^3/1000

10^9/L = Cells/µL/1000

10^9/L = 10^3/mm^3

10^9/L = K/µL

10^9/L = K/mm^3

10^9/L = Gpt/L

Results reported in other units will not be converted. All results will be displayed in a listing in their original units.

16 Other Outcome MRI Lesions

This analysis will be performed based on the FAS.

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

The number % of patients with the following lesions (as recorded in the MRI CRF page) will be summarised in a table:

- T1 gadolinium enhancing lesions
- T2 lesions (new)
- T2 lesions (enlarging)

All data collected on the MRI CRF page will be listed.

17 References

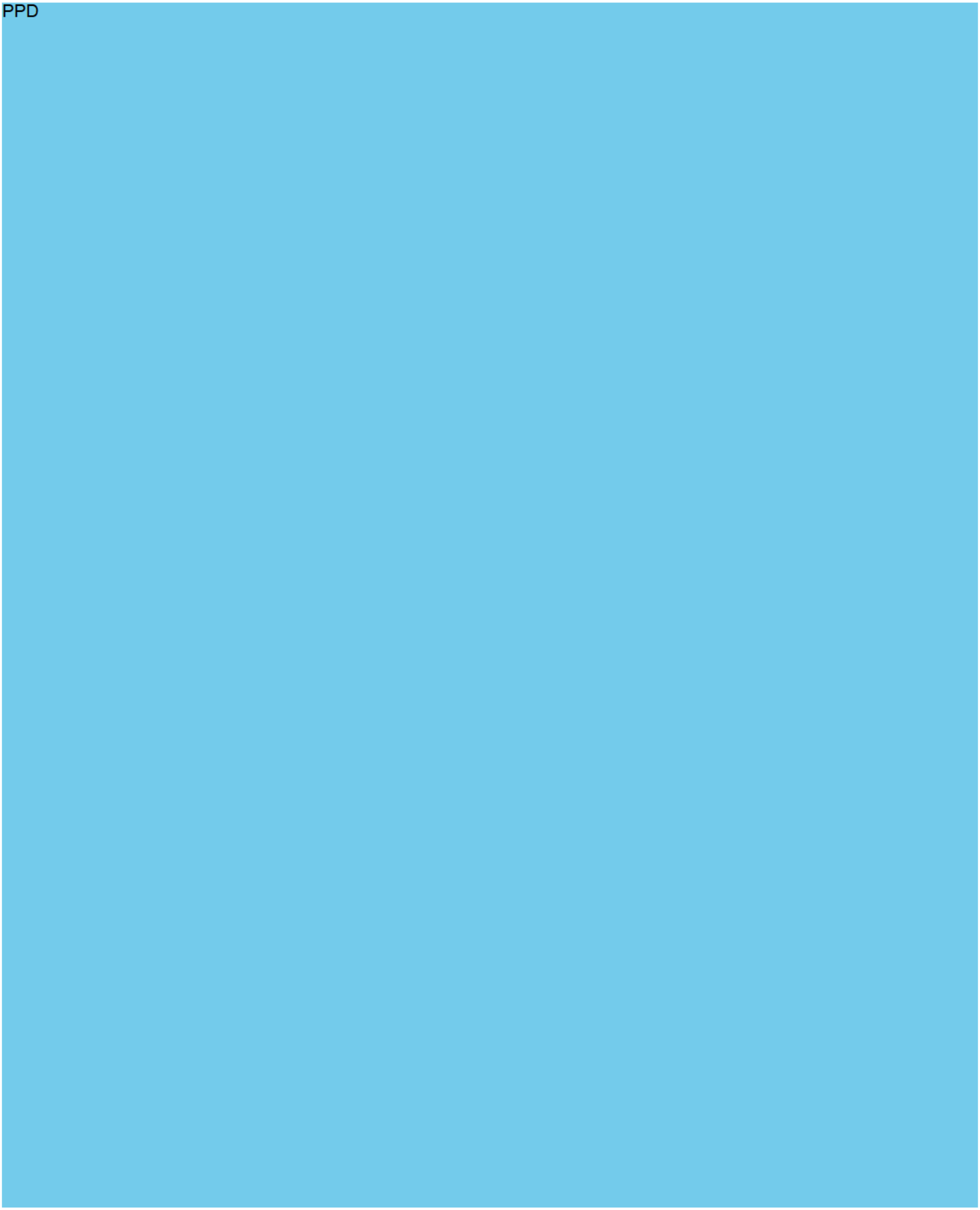
ICH E3 Structure and Content of Clinical Study Reports (Step 5, July 1996)

ICH E3 Structure and Content of Clinical Study Reports: Questions and Answers (R1) (January 2013)

ICH E9 Statistical Principles for Clinical Trials (Step 4, February 1998)

Fischer S, Proschmann U, Akgün K, Ziemssen T. Lymphocyte Counts and Multiple Sclerosis Therapeutics: Between Mechanisms of Action and Treatment-Limiting Side Effects. Cells. 2021 Nov 15;10(11):3177. doi: 10.3390/cells10113177. PMID: 34831400; PMCID: PMC8625745.

PPD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