Integrated Analysis Plan

Clinical Trial Protocol Identification No.	PPD
Title	**A 2-year prospective study to evaluate the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis**
Trial Phase	IV
Investigational Medicinal Product(s)	Mavenclad®
Clinical Trial Protocol Version	12 February 2019 / Version 2.0
Integrated Analysis Plan Author	**Coordinating Author** PPD **Function** / **Author(s) / Data Analyst(s)** PPD
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Integrated Analysis Plan Reviewers	**Function** / **Name** PPD

Signature Page

Integrated Analysis Plan: MS700568_0022

A 2-year prospective study to evaluate the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis

Approval of the IAP by all Merck Data Analysis Responsible is documented within Veeva Vault RIM. With the approval within Veeva Vault RIM, the Merck responsible for each of the analysis also takes responsibility that all reviewers' comments are addressed adequately.

Merck responsible	Date	Signature
PPD	Via Veeva Vault RIM approval process	

1 Table of Contents

2 List of Abbreviations and Definition of Terms

9HPT	9-Hole Peg Test
AE(s)	Adverse Event(s)
ARR	Annualized Relapse Rate
ARR_{qual}	Qualifying relapses in ARR
CC	Complete-Case
CDP	Confirmed Disability Progression
CI	Confidence Interval
CRF	Case Report Form
CCI	[redacted]
CSP	Clinical Study Protocol
CSR	Clinical Study Report
CT	Computed Tomography
CUA	Combined Unique Active
DMD	Disease Modifying Drug
dp	Decimal place
CCI	[redacted]
DTA	Data Transfer Agreement
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
ET	Early Termination
FAS	Full Analysis Set
CCI	[redacted]
FS	Functional System
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
HRA	High-relapse activity
IAP	Integrated Analysis Plan
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgG	Immunoglobulin G
IgM	Immunoglobulin M
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
IRC	Independent Review Charter
iRT	Interactive Response Technology
ITT	Intention-To-Treat
LLOQ	Lower Limit Of Quantification
KFS	Kurtzke Functional System
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTR	Magnetization Transfer Ratio
NCI-CTCAE	US National Cancer Institute Common Terminology Criteria for Adverse Events
NEDA	No Evidence of Disease Activity

NEPAD	No Evidence of Progression or Active Disease
CCI [redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ON	Optic Neuritis
PBVC	Percentage brain volume change
PDGMVC	Percentage deep grey matter volume change
PGMVC	Percentage grey matter volume change
PWMVC	Percentage white matter volume change
PML	Progressive Multifocal Leukoencephalopathy
PT	Preferred Term
Q1	25th Percentile
Q3	75th Percentile
RMS	Relapsing Multiple Sclerosis
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SOC	System Organ Class
SDTM	Study Data Tabulation Model
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1 Gd+	T1 gadolinium-enhancing
T25FW	Timed 25-Foot Walk
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
VZV	Varicella Zoster Virus
WHO-DD	World Health Organization Drug Dictionary
WOCBP	Women of Childbearing Potential

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	Date of last signature	PPD	New Document
2.0	Date of last signature	PPD	• Author and reviewers list updated • Tertiary endpoint: Ratio of Post-Baseline vs Baseline T1 Gd+ lesion count added to Interim and Final Analysis (see Section 14.3.3) • Tertiary Endpoint: T1 Gd+ lesion count > 0 added to Interim and Final Analysis (see Section 14.3.3) • Covariates: Time between scans (in Months) added (see Section 9) • Tertiary endpoint: Alternative covariance structures added (see Section 14.3)
3.0	Date of last signature	PPD	• Author and reviewers list updated • Definition of Treatment Periods updated (Section 9) • Additional analyses to describe the potential impact of the COVID-19 pandemic added (Section 9; 10.1; 10.2.1; 13; 15.2.3) • Updated MRI Baseline Characteristics (Section 11.2) • Added analysis Periods/analyses by Visits for MRI tertiary endpoints (Section 14.3) • Added MRI tertiary endpoints: new T1 GD+ lesions; total T2 lesions (Section 9; 14.3.3; 14.3.7) • Developed methods for tertiary endpoints (Section 14.3) • Analysis of fatigue TEAEs added (Section 15.2.3) • Instruction regarding missing date of start of medication removed (Section 9) • Definition of MRI activity updated (Section 14.3.12) • Added NEDA-4 (Section 14.3.12) • Added correlation analyses (Section 14.3.20) • Per-Protocol analysis set removed (Section 8.2) • Editorial changes to harmonize terminology • Handling of missing data in generalized model in tertiary analysis changed as it was discovered that it was also done differently from the specification of this IAP in the implementation of the sensitivity analysis (Section 14)

4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the primary analysis at the Month 6 interim analysis and the final analyses of data collected for protocol MS700568_0022. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP may be included in regulatory submissions or future manuscripts. Any post-hoc, or unplanned, analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon Section 8 (Statistics) 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. An additional Baseline analysis is planned once all subjects have completed Baseline assessments, which is not mentioned in the protocol and will be described and reported separately. CCI [redacted]

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	To determine the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis (RMS).	Differences in the counts of combined unique active (CUA) magnetic resonance imaging (MRI) lesions during the first 6 months (i.e., during Periods months 1-6, 2-6, 3-6) compared to Baseline (i.e., the Period from Screening to Baseline).	14.1
Secondary Objective	To assess the effect of Mavenclad® on different immune system composites in particular cell subtypes count and repopulation.	Characterization of immune cell subsets count at the end of 3, 6, 12, 15, 18 and 24 months compared to Baseline.	14.2
Tertiary Objectives	To assess the safety and tolerability of Mavenclad®.	• Occurrences of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) including and up to 24 months. • Lymphocyte count up to and including Month 24.	15
	To assess the effect of Mavenclad® on the progression of disability, cognition and incidence of relapse.	• Symbol Digit Modality Test (SDMT) • Expanded Disability Status Scale (EDSS) • Kurtzke Functional System (KFS) • 9-Hole Peg Test (9HPT) • Timed 25-Foot Walk (T25FW) • Annualized relapse rate (ARR) • Changes in CUA lesions • Number of CUA lesions • Changes in T1 Gd+ (T1 gadolinium-enhancing) lesion count • Volume changes of T1 Gd+ lesions • Number of T1 hypointense lesions • Change in volume of T1 hypointense lesions • Changes in active T2 lesion count • Responder rate during the different Periods as defined above with responder being defined as subjects with a CUA lesion count reduction of at least 1 • Changes in T2 lesion volume • Changes in Magnetization Transfer Ratio (MTR) • Changes in brain volume • No Evidence of Disease Activity (NEDA) • No Evidence of Progression or Active Disease (NEPAD)[redacted]	14.3
	[redacted]	[redacted]	4.3

6 Overview of Planned Analyses

The following analyses are planned for the study:

- Interim analysis after all subjects have completed the 6-month assessment,
- Final analysis at the end of the study.

In addition, a Baseline analysis has been performed. This Baseline analysis is not specified in the study protocol and is described in a separate Analysis Plan.

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6.1 Interim Analysis

An interim analysis for primary endpoint that includes all planned sensitivity analyses will be undertaken after all subjects have completed the 6-month assessment.

In addition, the Interim Analysis will describe the following characteristics of the study population up to the cut-off:

- Disposition of Participants and Discontinuations (Section 10.1),
- Major Protocol Deviations (Section 10.2),
- Demographics and Other Baseline Characteristics (Section 11):
  - Baseline Characteristics (Section 11.2),
  - Medical History (Section 11.1),
  - MS Disease Characteristics (Section 11.2),
  - Vital Signs (Section 11.2).
- Previous or Concomitant Medications/Procedures (Section 12),
- Treatment Compliance and Exposure (Section 13),

and will evaluate the following tertiary and safety endpoints up to 6 months Visit or the cut-off point:

- Number of CUA lesions during the Baseline and post-Baseline Periods (Section 14.3.2),

- T1 Gd+ lesion count by Visit and mean T1 Gd+ lesion count during the Baseline and post-Baseline Periods (Section 14.3.3),
- Changes in Standardized total active T2 lesion count during the post-Baseline Periods compared to the Baseline Period (Section 14.3.7),
- Responder rate during the different Periods (Section 14.3.8),
- Relapse reports including and up to the cut-off point (Number and Percentage of Subjects with (qualifying) relapses),
- Adverse Events (Section 15.1),
- Clinical Laboratory Evaluation (Section 15.3),
- Vital signs (Section 15.4).

The characteristics of the population as well as relapses will be summarized descriptively up to Month 6 Visit in the same way as for the final analysis. The tertiary MRI endpoints and Safety endpoints will be analyzed up to the Month 6 Visit or cut-off date in the same way as for the final analysis, as applicable.

Table 1 lists all assessments which will be included in the interim analysis.

Table 1: List of assessments included in the interim analysis

Assessments	Screening	Baseline	Month 1	Month 2	Month 3	Month 6
Informed Consent	X					
Demographics	X					
Weight		X	X			
Vital Signs	(X)	X				
Medical History	X					
Disease History	X					
Relapse History		X				
MRI	X	X	X	X	X	X
Disability (EDSS/KFS)	X	X				
Relapse count			X	X	X	X
Lymphocyte Count	X			X		X
Treatment Administration		X	X			
AEs		X	X	X	X	X
Concomitant medications and procedures	X	X	X	X	X	X
Relevant previous medications	X					

Assessments	Screening	Baseline	Month 1	Month 2	Month 3	Month 6
Serology (incl. Varicella and TB)	X					
Pregnancy test	X	X				
Study termination		X	X	X	X	X

Data cleaning will be undertaken on all data involved in interim reporting. Details and level of data cleaning will be documented in data management plans.

6.1.1 Cut-off date

Only data up to the Month 6 Visit of each subject will be analyzed in the interim analysis. Therefore, the cut-off date is defined as the maximum Month 6 Visit date (i.e., date of the last assessment for the Month 6 Visit). For subjects with a missing Month 6 Visit the cut-off date will be 180 days after start of study medication. This includes subjects who discontinued before Day 180.

- Cut-off date (Month 6 Visit done) = Maximum Month 6 Visit date,
- Cut-off date (Month 6 Visit not done) = Start of study medication + 180 days - 1.

All occurrences of death will be included in the interim analysis regardless of the timepoint (i.e., any death that is included in the database at the time of the snapshot will be reported in the interim analysis).

6.1.2 Data handling after cut-off date

Data after cut-off do not undergo the cleaning process.

Data other than the date of death obtained after the cut-off will not be displayed in any listings or used for summary statistics.

If the stop date for an AEs is after the date of cut-off, the AEs will be considered as ongoing during the Interim Analysis.

6.2 Final Analysis

The final analysis will include all described analyses of this IAP apart from the efficacy analyses already performed for the primary analysis at the 6 months Interim Analysis. The final analysis will be based on all data available in the database at the time of the final database lock.

7 Changes to the Planned Analyses in the Clinical Trial Protocol

The following decision was made prior to the last enrolled subject starting study treatment, with post-treatment data unavailable at the time of the decision making:

Primary analysis will be complemented by a non-parametric analysis methods as a data review of Baseline data has shown that the primary endpoint (Differences in the counts of CUA MRI lesions during the first 6 months, that is, during Period months 1-6, 2-6, 3-6, compared to Baseline, from Screening to end of Baseline assessment), does not follow Normal distribution.

Other decisions applied after the primary analysis was performed:

Handling of data of subjects with a delayed 2nd treatment course:

> The study protocol provides the following guidance how data of subjects with a delayed 2nd treatment course beyond 3 months should be handled in the statistical analyses.
>
> Section 8.5.1: "Subjects for whom treatment is delayed by over 3 months may not have all assessment data captured and as such, these observations will be treated as missing."
>
> As the data of the 1st treatment course are expected to provide valid efficacy information and the treatment delay of the 2nd year does not affect the 1st year course, it is decided that all data from the 1st treatment course should be included in all efficacy analyses while data from the 2nd treatment course will be excluded from all efficacy analyses for subjects with a delayed 2nd treatment course beyond three months.
>
> For safety analyses, all data from both Treatment Courses will be used independently from the delayed start of Treatment Course 2. Section 9 defines the details of the data handling of subjects with a Delayed Treatment Course 2.

Tertiary endpoints:

> Additional endpoints have been added and endpoints wording aligned according to the latest data transfer specification, where applicable.

Analyses of Magnetization Transfer Ratio (MTR):

> The Tertiary Endpoint in the Section 4.3.1 of the protocol, "Changes in Magnetization Transfer Ratio (MTR) at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to Baseline" were listed.
>
> Since MTR results will be used in parallel with brain atrophy results measured by MRI, which are comparing Month 24 with Baseline and Month 6 MRI scans, thus changes in MTR at the end of 1, 2, 3, 6, 12, 15, and 18 months compared to Baseline are not provided by central reading.

COVID-19 pandemic:

> Additional analyses to describe the potential impact of the COVID-19 pandemic added.

Analysis of Responder rate:

The study protocol lists one of the Tertiary Endpoints in Section 4.3.1 as follows: "Responder rate during the different periods as defined above with responder being defined as subjects with a CUA lesion count reduction of at least 1".

The definition of responders refers to Standardized CUA lesion count and will thus be reported only for those periods for which standardized CUA lesion count is reported as well.

Terminology:

Wording of endpoints simplified and aligned to be consistent with standards.

8 Protocol Deviations and Analysis Sets

8.1 Definition of Protocol Deviations

Major protocol deviations are protocol deviations (PD) that might significantly affect the completeness, accuracy, and/or reliability of the study data, or that might significantly affect a subject's rights, safety, or well-being.

Major protocol deviations and any action to be taken regarding the exclusion of subjects, or affected data from specific analyses, are defined in the project-specific Protocol Deviation Specification.

All protocol deviations are documented in Study Data Tabulation Model (SDTM) datasets whether identified through site monitoring, medical review or programming. Tables and listings of PDs are defined in Section 10.2.

8.2 Definition of Analysis Sets and Subgroups

Enrolled Set (ES)

All subjects enrolled in the study, i.e., all subjects with a signed informed consent.

Intent-to-treat Set (ITT)

All subjects classified as eligible (i.e., medication assigned by iRT at the Baseline Visit).

Full Analysis Set (FAS)

All subjects in the ITT treated with at least one dose of study medication.

Treatment Completer Set – Year 1 (TCS-1)

All subjects from the FAS who completed the full Treatment Course of the first year (Treatment Course 1). Subjects will be classified as Treatment Completer for the first year if they have a compliance greater than or equal to 100% for Treatment Course 1.

Treatment Completer Set – Year 2 (TCS-2)

All subjects from the FAS who completed the full Treatment Course of the first and the second year. Subjects will be classified as Treatment Completer for the second year if they have a compliance greater than or equal to 100% for Treatment Course 1 and Treatment Course 2 and received the treatment without delay (see Section 9 for definition).

Safety Analysis Set (SAF)

All subjects treated with at least one dose of study medication.

Unless otherwise specified, all efficacy analyses will be performed on the FAS.

Some tertiary analyses will be repeated on the Treatment Completer Sets and the primary analysis, on the ITT (if different from FAS), to evaluate the robustness of the primary results to deviations of the planned treatment regimen. Further details are given in the respective sections. All safety analyses will be performed on the SAF.

Additional Subgroup or Subset Analysis Sets

Subgroup analyses will be performed on subgroups as defined below.

- High-relapse activity (HRA)
    - HRA: at least 2 relapses in the previous year (i.e. the number of historical relapses within 12 months prior to Baseline ≥2) regardless of prior use of DMDs
    - Non-HRA: otherwise

  Unless otherwise indicated, all descriptive statistical analyses will be presented separately for the HRA subgroups.

- Previous treatment with Disease Modifying Drugs (DMDs):
    - DMD pre-treated: Subjects will be categorized as DMD pre-treated if they have taken DMDs any time before start of study medication. Details of the definition of DMDs are specified in Appendix 1 (Section 18.1).
    - Pre-treatment naïve: all subjects not classified as DMD pre-treated.

The primary analysis and selected demographic and background characteristics as well as selected tertiary analyses will be repeated for these subgroups.

The following subset(s) are defined:

- Baseline Period CUA count > 0 (i.e. all subjects with a CUA lesion count > 0 during the Baseline Period)

  As subjects with a CUA count of 0 during the Baseline Period cannot show an improvement in the number of CUA lesions during the study, some of the efficacy analyses will be repeated for this subset that has at least one CUA lesion during the Baseline Period.

9 General Specifications for Data Analyses

Treatment groups

The treatment group will be labeled as Mavenclad®.

Significance level

The three hypotheses of the primary analysis (see Section 14.1) will be tested as one -sided, on a 2.5% significance level. The testing procedure will stop as soon as one of the hypotheses cannot be rejected following a pre-specified order. Due to this sequential order of tests an adjustment for a potential type-I-error inflation due to the multiple testing is not required.

CCI [redacted] All statistical tests will be performed two-sided. If confidence intervals are to be calculated, these will be two-sided with a confidence probability of 95%, unless otherwise specified in this IAP.

Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics, i.e., number of subjects, number of subjects with missing and non-missing values, mean with standard deviation, median, 25th Percentile - 75th Percentile (Q1-Q3), minimum, and maximum.

Qualitative variables will be summarized by counts and percentages.

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

In case where the analysis refers only to certain Visits, percentages will be based on the number of subjects still present in the study at that Visit, unless otherwise specified.

Definition of Baseline

The last non-missing measurement prior to start of study medication will serve as the Baseline measurement. Measurements performed on the day of first intake of study medication are assumed to be “prior to start of study medication”, as long as it has not been confirmed that the procedure was performed afterwards. This assumption is justified as following the sequence of procedures as specified in the study protocol. The intake of study medication should be the last procedure on the Visit day.

The MRI scans will be reconciled during central MRI review process. Therefore, MRIs will be considered as Baseline MRIs if assigned to the Baseline Visit by the central imaging review.

Definition of Study Periods

- Baseline Period: The Baseline Period is defined as the Period between the Screening and the Baseline MRI scan.
- Post-Baseline Period: The post-Baseline Periods that are used in the primary analysis are defined as follows:
  - Period 1 (p_1) is defined as the Period between Month 1 and Month 6 MRI scans.
  - Period 2 (p_2) is defined as the Period between Month 2 and Month 6 MRI scans
  - Period 3 (p_3) is defined as the Period between Month 3 and Month 6 MRI scans

  In addition, the following post-Baseline Periods are defined solely for tertiary analyses:

  Three months Periods

  - Period 3.1 ($p_{3.1}$) is defined as the Period between Baseline and Month 3 MRI scans.

  Six months Periods

  - Period 6.1 ($p_{6.1}$) is defined as the Period between Baseline and Month 6 MRI scans,
  - Period 6.2 ($p_{6.2}$) is defined as the Period between Month 6 to Month 12 MRI scans,
  - Period 6.3 ($p_{6.3}$) is defined as the Period between Month 12 to Month 18 MRI scans,
  - Period 6.4 ($p_{6.4}$) is defined as the Period between Month 18 to Month 24 MRI scans.

  Periods excluding the Period between the Baseline scan and the Month 1 MRI scan:

  - Period 11.1 ($p_{11.1}$) is defined as the Period between Month 1 to Month 12 MRI scans,
  - Period 11.2 ($p_{11.2}$) is defined as the Period between Month 1 to Month 24 MRI scans.

  Yearly Periods:

  - Period 12.1 ($p_{12.1}$) is defined as the Period between Baseline to Month 12 MRI scans,
  - Period 12.2 ($p_{12.2}$) is defined as the Period between Month 12 to Month 24 MRI scans.

  2 -Year Period:

  - Period 24.1 ($p_{24.1}$) is defined as the Period between Baseline to Month 24 MRI scans.

  Sequential Visit Periods

  - Period 100.0 ($p_{100.0}$) is defined as the Period between Screening and Baseline (equivalent to Baseline Period) MRI scans
  - Period 100.1 ($p_{100.1}$) is defined as the Period between Baseline and Month 1 MRI scans,

- Period 100.2 ($p_{100.2}$) is defined as the Period between Month 1 and Month 2 MRI scans,
- Period 100.3 ($p_{100.3}$) is defined as the Period between Month 2 and Month 3 MRI scans,
- Period 100.6 ($p_{100.6}$) is defined as the Period between Month 3 and Month 6 MRI scans,
- Period 100.12 ($p_{100.12}$) is defined as the Period between Month 6 and Month 12 MRI scans,
- Period 100.15 ($p_{100.15}$) is defined as the Period between Month 12 and Month 15 MRI scans,
- Period 100.18 ($p_{100.18}$) is defined as the Period between Month 15 and Month 18 MRI scans,
- Period 100.24 ($p_{100.24}$) is defined as the Period between Month 18 and Month 24 MRI scans.

Note: Period start and end dates are defined by the MRI dates as provided by central reading.

Definition of change from Baseline

Change from Baseline = Visit value – Baseline value.

Percentage Change from Baseline = 100 × (Visit value – Baseline value) / Baseline value.

The Percentage Change from Baseline will be set to missing for subjects with a zero at Baseline.

Definition of Visit dates

The Visit start date is the date of the first assessment which belongs to the corresponding Visit.

The Visit end date is the date of the last assessment which belongs to the corresponding Visit.

Definition of duration

Duration will be calculated by the difference of start and stop date + 1, in days (unless specified otherwise).

Treatment Period

The treatment Period begins with the start of study medication on Study Day 1 and continues through to the completion of the treatment Period at the Month 24 Visit (see CSP, Section 7.1.2). Start of study medication is the date of first intake of study medication. Start of study medication in Year 2 is the date of first intake of study medication at or after the Month 12 Visit.

Treatment Period:

- Start = Start of study medication,
- End = Visit end date of Month 24 Visit, or Early Termination (ET) Visit, in case of early discontinuation, or the study discontinuation date, if the ET Visit was not performed.

Course 1 Treatment Period:

- Start = Start of study medication,
- End = Start of study medication at or after the Month 12 Visit - 1 day, or if the subject did not receive Treatment Course 2: Start of study medication of Treatment Course 1 + 457 days (which is obtained by 360 (12 months) + 90 (3 months) + 7 (Visit window)) or date of discontinuation, if earlier.

Course 2 Treatment Period:

- Start = Start of study medication at or after the Month 12 Visit,
- End = End of Treatment Period.

Definition of Delayed Treatment Course 2

The Treatment Course 2 will be defined as delayed, if the start of study medication is delayed by more than 3 months (= 90 days) or did not start at all i.e.:

- Start of Study medication of Treatment Course 2 > Start of Study Medication of Treatment Course 1 + 457 days (which is obtained by 360 (12 months) + 90 (3 months) + 7 (Visit window)), or
- Treatment Course 2 never started (i.e., no study medication taken at or after the Month 12 Visit).

Data handling in case of a Delayed Treatment Course 2

For subjects with a Delayed Treatment Course 2, only data observed during the Course 1 Treatment Period will be analyzed in all efficacy analyses. Efficacy data after the Course 1 Treatment Period will be counted as missing in the statistical analyses and marked in the listings. In all efficacy analyses defined by Period, the subject will be classified as if the subject discontinued at the end of the Course 1 Treatment Period. For subjects without a delay the whole Treatment Period will be analyzed.

For all other analyses (except efficacy) the data is not limited to the Course 1 Treatment Period for subjects with a Delayed Treatment Course 2.

Definition of start of COVID-19-Pandemic

The start of COVID-19 pandemic will be defined by country as the earliest date of either the date of the first death from COVID-19 occurred in each country according to the published data by European Centre for Disease Prevention and Control on 26th June 2020 (https://www.ecdc.europa.eu/en/publications-data/download-todays-datageographic-distribution-covid-19-cases-worldwide) or 11th March 2020 (when the WHO declared COVID-19 pandemic).

Visit timing with respect to COVID-19 pandemic

A Visit is defined to be performed after the start of COVID-19 pandemic if the Visit end date is greater than the start of COVID-19 pandemic date.

Conversion factors

The following conversion factors will be used to convert days into months or years for all observations except Visit related dates:

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

Time window

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

The Visit schedule is defined as follows:

- 1 month = 30 days,
- 1 year = 360 days,

relative to the start date of the Baseline Visit for Treatment Course 1 and relative to the start date of the Month 12b Visit as defined in the eCRF (see also Section 15.3) for Treatment Course 2.

In each analysis, should assessments be delayed, subjects' assessment data will be treated as though it occurred at the time point specified (i.e., out of Visit windows will be not excluded or adjusted for any analyses) and inferences will be conducted accordingly. Thus, further time windows will not be specified.

All observations from unscheduled Visits will be included only in the analyses of Visit independent summaries (e.g. counts of events, progressions or worst value during Treatment Period) unless for the unscheduled Visits prior to start of study medication and the last assessment available. In case of unscheduled Visits prior to start of study medication, these will be considered to define Baseline. In the last missing case the ET Visit will be imputed by the unscheduled Visit.

The assessments of the ET Visit will be mapped to the nearest planned post-Baseline Visit with a missing assessment before or after the ET Visit of the individual assessment for all statistical analyses and descriptive summaries. As not all assessments of the ET are performed at each Visit, the different assessments of the ET can be assigned to different Visits. If the duration (in days) between the ET Visits and two missing planned Visits are equal, then the assessment will be assigned to the later Visit.

Handling of missing data

Unless otherwise specified in respective sections, missing data will not be replaced.

The handling of missing covariate and stratification factor information is described below.

The handling of missing DMD end date is described in Section 12.

Incomplete or missing onset dates of relapses from "MS Relapse Report" will be imputed as follows:

- In cases where the onset date is partially missing but the onset month and year, or the onset year are equal to the start of study medication or the date is missing then the onset date will be replaced by the start date of study medication.
- In all other cases the missing onset day or missing onset month will be replaced by 1 (but not before start of study medication).

In all subject data listings, imputed values will be presented and flagged.

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

Where tables are presented over time, the total number of subjects with missing and non-missing observations at each time-point should reflect the population still in the study at that time. This does not apply when imputations are made beyond study withdrawal.

Data Handling for MRI data

Data handling of Primary endpoint(s) and its components:

The MRI lesions will be evaluated by independent central review, which will provide the following measurements for the primary endpoints (see IRC for Counting Brain MRI Lesions [3]):

- Total number of T1 Gadolinium enhancing lesions (T1 Gd+) (or Not Evaluable [NE], if applicable) at the first and last MRI of the respective Period,
- Total number of new T2 lesions with T1 Gd+ (or NE, if applicable) of the respective Period (comparing the last with the first MRI of the respective Period),
- Total number of enlarging T2 lesions with T1 Gd+ (or NE, if applicable) of the respective Period (comparing the last with the first MRI of the respective Period),
- Total number of new T2 lesions without T1 Gd+ (or NE, if applicable) of the respective Period (comparing the last with the first MRI of the respective Period),
- Total number of enlarging T2 lesions without T1 Gd+ (or NE, if applicable) of the respective Period (comparing the last with the first MRI of the respective Period).

The statistical analysis will use the results from the Global assessment (i.e. Readtype=GLOBAL).

The assignment of MRIs to the respective Visits (e.g. assignment of ET MRIs or delayed MRIs due to steroid treatment) will be ensured by the central reading process. MRIs taken while on Steroid Treatment as identified as a major PD will be excluded from the analysis.

All derived lesion counts (except for the Mean T1 Gd+ lesion count) as specified below will be classified as NE if one of the components required for the calculation has been classified as NE by the central reading. The Mean T1 Gd+ lesion count will be set to NE only, if all T1 Gd+ lesion counts that correspond to the respective Period are classified as NE. In all other cases the mean will be calculated based on the available counts during the respective Period.

T1 Gd+ lesion count

As with this procedure a Visit is assessed multiple times for the T1 Gd+ and thus T1 Gd+ will be reported multiple times per Visit, the value for a Visit of the earliest available Period will

be selected for the statistical analysis. As the Global Review will ensure that all duplicates have identical lesion count, this rule does not have an impact on the number of T1 Gd+ but defines further attributes (e.g. date of review).

The T1 Gd+ counts for a Period will be defined as the sum of the T1 Gd+ lesions from all scheduled MRI scans reported for a Visit that is included in a Period divided by the actual number of MRI scans with a reported lesion count (i.e. not NE) during a Period.

- T1 Gd+ lesion count (by Visit) = T1 Gd+ lesions count from the MRI at the respective Visit

- Mean T1 Gd+ lesion count (by Period) = T1 Gd+ lesion count during the Period / # of scans belonging to the respective Period with non-missing T1 Gd+ lesion count.

MRIs are assigned to a Period as follows:

- Baseline Period:
  - Screening Visit
  - Baseline Visit

- Period 1:
  - Month 1 Visit
  - Month 2 Visit
  - Month 3 Visit
  - Month 6 Visit

- Period 2:
  - Month 2 Visit
  - Month 3 Visit
  - Month 6 Visit

- Period 3:
  - Month 3 Visit
  - Month 6 Visit

Active T2 lesion count

As the new or enlarging T2 lesion count depends on the length of the Period, it will be presented as reported (non-standardized) and standardized to 1 months (30.4375 days):

- Period length (days) = MRI date at end of Period – MRI date at start of Period +1,
- Standardized total T2 lesion count (by Period per 1 months) = Total number of T2 lesions per Period * 30.4375 / Period length.

The following types of T2 lesions are defined per Period (standardized and non-standardized):

- Total new T2 lesion count =
  Total number of new T2 lesions with T1 Gd+
  + Total number of new T2 lesions without T1 Gd+
- Total enlarging T2 lesion count =
  Total number of enlarging T2 lesions with T1 Gd+
  + Total number of enlarging T2 lesions without T1 Gd+,
- Total active T2 lesion count =
  Total new T2 lesion count
  + Total enlarging T2 lesion count

The total active T2 Lesion count will also be reported for the Baseline, Month 2, Month 3, and Month 6 Visit and is defined as:

- Total active T2 Lesion count = Total number of new or enlarging T2 lesions since the scan of the previous Visit

and will be calculated as follows:

- Total active T2 Lesion count at the Baseline Visit
  = Total active T2 Lesion count of the Baseline Period
- Total active T2 Lesion count at the Month 2 Visit
  = Total active T2 Lesion count of Period 1 (M1-M6) – Period 2 (M2-M6)
- Total active T2 Lesion count at the Month 3 Visit
  = Total active T2 Lesion count of Period 2 (M2-M6) – Period 3 (M3-M6)
- Total active T2 Lesion count at the Month 6 Visit
  = Total active T2 Lesion count of Period 3

For the calculation of the CUA lesion count, only T2 lesions that did not emerge from a T1 Gd+ lesion will be taken into account.

- Total active T2 lesion count (without T1 Gd+) =
  Total new T2 lesion count without T1 Gd+
  + Total enlarging T2 lesion count without T1 Gd+

and will be standardized to the length of the Period. Total active T2 lesion count (without T1 Gd+) will only be calculated if T1 Gd+ counts for beginning and end of the corresponding Period are non-missing.

CUA lesion count

The number of CUA lesions for a Period will be defined as the sum of the T1 Gd+ and new or enlarging T2 counts for the respective Period and will be standardized to one scan (for T1) or one month (for T2) to harmonize the units of the 2 assessments.

$\#CUA(p_i)$ = Standardized CUA lesion count (by Period i per 1 month)
= Mean T1 Gd+ lesion count (by Period i per Visit)

+ Standardized total active T2 lesion count (without T1 Gd+)
(by Period i per 1 months)

The CUA lesion count will only be calculated if both components (T1 and T2) are non-missing.

Data handling of Tertiary endpoints:

The MRIs will be evaluated by independent central review (see IRC for Lesion Counting for the Tertiary Endpoint [6]). As the central reading process for Tertiary MRI Endpoints is different from the process for Primary MRI Endpoints, data are provided in a different format (see Data Transfer Specification [8]).

The assignment of MRIs to the respective Visits will be ensured by the central reading process and may differ from the initial MRI Visit assignments as reported in the eCRF. The statistical analysis is based on the MRI assignments as provided by central reading.

All derived lesion counts (except for the Mean T1 Gd+ lesion count) as specified below will be classified as NE if one of the components required for the calculation has been classified as NE by the central reading. The Mean T1 Gd+ lesion count will be set to NE only, if all T1 Gd+ lesion counts that correspond to the respective Period are classified as NE. In all other cases the mean will be calculated based on the available counts during the respective Period.

T1 Gd+ lesion count

- The T1 Gd+ are defined as follow: T1 Gd+ lesion count (by Visit) = T1 Gd+ lesions count from the MRI at the respective Visit.

- Mean T1 Gd+ lesion count (by Period) = sum of all T1 Gd+ lesion counts during the Period / # of scans belonging to the respective Period with non-missing T1 Gd+ lesion count.
  All MRI scans belong to a Period that either have been performed during the Period including start and end. For post-Baseline periods starting at Baseline, the Baseline Visit will not be included. For example, Period 6.1 will include Month 1, 2, 3, 6 Visit, Period 24.1 will include all MRI scans except Screening and Baseline Visit).

- New T1 Gd+ lesion count (by Period) = number of new T1 Gd+ lesion counts from the comparison of the two selected MRI scans performed by central reading according to the Data Transfer Specification [8] (e.g. for Period 6.1 comparison of the MRI scans from Baseline Visit and Month 6 Visit will be performed)

Active T2 lesion count

As the active (i.e the new or enlarging) T2 lesion count depends on the length of the Period, it will be presented as reported (non-standardized) and annualized (standardized to 1 years (365.25 days)):

- Period length (days) = MRI date at end of Period – MRI date at start of Period +1,
- Annualized active T2 lesion count (by Period) = Total number of active T2 lesions per Period * 365.25/ Period length.

The following types of T2 lesions are defined per Period (standardized and non-standardized):

- Total new T2 lesion count =
  Total number of new T2 lesions with T1 Gd+
  + Total number of new T2 lesions without T1 Gd+
- Total enlarging T2 lesion count =
  Total number of enlarging T2 lesions with T1 Gd+
  + Total number of enlarging T2 lesions without T1 Gd+,
- Total active T2 lesion count =
  Total new T2 lesion count
  + Total enlarging T2 lesion count

Note: the number of new or enlarging T2 (with and without T1 Gd+) will be provided by central reading for each of the Periods including the Sequential Visit Periods, except for Period 3.1. For Period 3.1, the sum of the Sequential Visit Periods 100.1, 100.2 and 100.3 will be calculated.

For the calculation of the CUA lesion count, only T2 lesions that did not emerge from a T1 Gd+ lesion will be taken into account.

- Total active T2 lesion count (without T1 Gd+) =
  Total new T2 lesion count without T1 Gd+
  + Total enlarging T2 lesion count without T1 Gd+

and will be standardized to the length of the Period (i.e. annualized). Total active T2 lesion count (without T1 Gd+) will only be calculated if T1 Gd+ counts for beginning and end of the corresponding Period are non-missing.

CUA lesion count

The number of CUA lesions for a Period will be defined as the sum of the T1 Gd+ and new or enlarging T2 counts for the respective Period and will be standardized to one scan (for T1) or one year (for T2) to harmonize the units of the 2 assessments.

$\#CUA(p_{post\text{-}Baseline})$ = Annualized CUA lesion count (by post-Baseline Period per 1 year)
= Mean T1 Gd+ lesion count (by Period i)
+ Annualized total active T2 lesion count (without T1 Gd+)
(by Period i per 1 year) Different from the primary analysis, T2 lesion count will be standardized to 1 year instead of 1 month due to longer periods and for comparison with other studies,

The CUA lesion count will only be calculated if both components (T1 and T2) are non-missing.

Data Handling in case of major PDs

PDs will not be considered in the planned statistical analyses (i.e., all data will be analyzed independent from any reported PD) except for PD due to MRI taken during steroid treatment (MRI will be excluded from the primary analysis).

Covariates and stratification factors

Age

Age (years) at time of Informed Consent (loaded from iRT). Missing age will be replaced as follows if used as a covariate:

- Age will be estimated from the year of birth (year of IC – year of birth), as recorded in the electronic Case Report Form (eCRF),
- If year of birth is missing, age will be imputed by the mean age of the FAS.

EDSS at Baseline

Expanded Disability Status Scale (EDSS) at Baseline will be categorized by:

- ≤3 (reference),
- >3.

Missing EDSS at Baseline will be imputed by the median Baseline EDSS of the FAS if used as a stratification factor.

Pooled centers

Some centers will have few eligible subjects only. Therefore, the centers will be pooled together by country except for

- sites that have more than 12 subjects in the FAS (i.e. these sites will not be pooled with any other site).
- for countries that have 6 subjects or less in the FAS that will be pooled as follows:
- Scandinavia = Finland and Sweden
- Mediterrannea = Italy and Spain
- Austria-Hungary = Austria and Hungary

MRI specific covariates

Time between scans: in Months

Time between scans (in Months) is calculated as follows:

- Time between scans (in Months) = (MRI date of the Visit - MRI of the previous Visit + 1) /30.4375. i.e.:
    - If (Visit=Month 1) then Time between scans (in Months) = (MRI date at Month 1 - MRI date at Baseline + 1)/ 30.4375
    - If (Visit=Month 2) then Time between scans (in Months) = (MRI date at Month 2 - MRI date at Month 1 + 1)/ 30.4375
    - If (Visit=Month 3) then Time between scans (in Months) = (MRI date at Month 3 - MRI date at Month 2 + 1)/ 30.4375
    - If (Visit=Month 6) then Time between scans (in Months) = (MRI date at Month 6 - MRI date at Month 3 + 1)/ 30.4375

If the corresponding MRI is available and the time between scans is missing (due to preceding MRI being missing) it will be replaced by expected time as follows:

- Month 1/2/3 Visit =1
- Month 6 Visit =3.

Time between scans: in Years

Time between scans (in Years) is calculated as follows:

- Time between scans (in Years) = (MRI date of the Visit - MRI of the previous Visit + 1) /365.25, i.e.:
  - If (Visit= Month 1) then Time between scans (in Years) = (MRI date at Month 1 - MRI date at Baseline + 1)/ 365.25
  - If (Visit= Month 2) then Time between scans (in Years) = (MRI date at Month 2 - MRI date at Month 1 + 1)/ 365.25
  - If (Visit= Month 3) then Time between scans (in Years) = (MRI date at Month 3 - MRI date at Month 2 + 1)/ 365.25
  - If (Visit= Month 6) then Time between scans (in Years) = (MRI date at Month 6 - MRI date at Month 3 + 1)/ 365.25
  - If (Visit= Month 12) then Time between scans (in Years) = (MRI date at Month 12 - MRI date at Month 6 + 1)/ 365.25
  - If (Visit= Month 15) then Time between scans (in Years) = (MRI date at Month 15 - MRI date at Month 12 + 1)/ 365.25
  - If (Visit= Month 18) then Time between scans (in Years) = (MRI date at Month 18 - MRI date at Month 15 + 1)/ 365.25
  - If (Visit= Month 24) then Time between scans (in Years) = (MRI date at Month 24 - MRI date at Month 18 + 1)/ 365.25

If the corresponding MRI is available and the time between scans is missing (due to preceding MRI being missing) it will be replaced by expected time as follows:

- Month 1/2/3 Visit =1
- Month 6 Visit =3
- Month 12 Visit =6
- Month 15 Visit =3
- Month 18 Visit =3
- Month 24 Visit =6.

Software(s)

All analyses will be performed using SAS® Software version 9.3, or higher.

10 Trial Participants

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

10.1 Disposition of Participants and Discontinuations

Subject disposition will be presented for the ES:

- Total number of subjects enrolled (i.e., subjects who gave informed consent),
- Number of subjects who discontinued from the study prior to treatment overall and grouped by the main reason (i.e., the Reason why the subject did not continue beyond screening, as recorded in the CRF. If the Subject did not meet all Eligibility Criteria, the failed specific inclusion or exclusion criteria will be provided in addition). Subjects not classified as screened failure but without treatment assignment by the iRT will be listed as "no treatment assigned",
- Number of eligible subjects (i.e., subjects with treatment assignment by the iRT system),
- Overall and by Treatment Course, who received at least dose one of study medication,
- Who discontinued the study medication, grouped by main reason (according to the information on the Study Termination CRF page),
- Who completed the study (according to the information on the Study Termination CRF page).
- Number of Visits performed before and after Start of COVID-19 pandemic

Percentages will be presented with respect to the number of eligible subjects. The number of subjects in each analysis set will be provided overall, by region, by country within region, and by site.

The following subject data listings will be provided:

- Listing of discontinued subjects for the ITT,
- Listing of subjects excluded from the Analysis Sets.

The number of subjects with least one available T1 GD+ lesion count, T2 lesion count and CUA lesion count for each Study Period will be presented for the FAS together with the statistics for the length of the Study Periods, and statistics of the number of available T1 Gd+ lesion counts during the Study Periods.

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

The following summary tables and listings of major protocol deviations (see Section 8.1 for details) will be provided by Inclusion/Exclusion and other deviations for the ITT:

- Frequencies per reason of major protocol deviations (overall and based on relationship to COVID-19 pandemic),
- Listing of major protocol deviations (including information regarding relationship to COVID-19 pandemic).

11 Demographics and Other Baseline Characteristics

Unless stated otherwise, summaries will be presented on the FAS.

11.1 Medical History

The medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Summary table will be presented by primary system organ class (SOC) and preferred term (PT).

11.2 Other Baseline Characteristics

11.3 Demographics

Demographic characteristics will be summarized using the following information from the Screening/Baseline Visit CRF pages.

Demographic characteristics:

- Gender:
  - Male,
  - Female,
  - Missing.
- Race:
  - White,
  - Black or African American,
  - Asian,
  - American Indian or Alaska Native,
  - Native Hawaiian or Other Pacific Islander,
  - Other,
  - Not collected at this site,
  - Missing.
- Ethnicity Hispanic or Latino:
  - Yes,
  - No,
  - Missing.
- Ethnicity Japanese:
  - Yes,
  - No,
  - Missing.

- Age (years)
- Age categories:
  - ≤ 40 years,
  - 40 years, < 65 years,
  - ≥ 65 years,
  - Missing.
- Region:
  - Eastern & Central Europe: Austria, Germany, Hungary, Poland, Czech Republic
  - Scandinavia: Finland, Sweden
  - Mediterranea: Italy, Spain
  - Western Europe: France, United Kingdom
  - Australia,
  - Canada,
  - Israel.
- Country
  - Country 1
  - …
- Pooled Centers

The following subject data listing will be provided:

- Demographic Data (Country, Sex, Race, Age, EDSS at Baseline, Number of relapses within 12 months prior to Baseline).

MS Disease Characteristics

The duration since onset and diagnosis of MS at Baseline in months, as well as the EDSS at Baseline, will be presented. In addition, the number of subjects grouped by the major systems affected (at onset of MS) will be presented.

- Time since onset of MS (months) = (Visit start date of Baseline Visit - date of first symptom + 1) / 30.4375,
- Time since diagnosis (months) = (Visit start date of Baseline Visit - date of diagnosis + 1) / 30.4375,
- Time since first relapse (months) = (Visit start date of Baseline Visit - date of first relapse + 1) / 30.4375,

- Number of previous DMDs (i.e., number of different PTs of DMDs as entered into the "Relevant Previous Medication Form" (see Appendix 1)),
  - 0
  - 1
  - 2
  - >2
- EDSS at Baseline,
- EDSS at Baseline,
  - ≤3
  - >3
  - Missing
- Number of historical relapses within 12 months prior to Baseline (i.e., number of relapses from the "MS Relapse History Baseline" eCRF page):
  - Baseline Visit Start Date ≥ onset date ≥ Baseline Visit Start Date - 396 Days, if the day of the onset is available,
  - Month of the Baseline Visit Start Date ≥ onset month ≥ month of Baseline Visit Start Date – 13 months, if only the month of onset is available.
- Number of historical relapses within 12 months prior to Baseline categorized to:
  - 0
  - 1
  - 2
  - >2
- High-relapse activity (HRA)
  - Yes
  - No

Missing days or months of the dates of first symptom, diagnosis, first relapse will be replaced by 1.

MRI Baseline Characteristics

The following selected results of the independent MRI review for the Baseline Period will be presented:

T1 Gd+ lesions:

- Mean T1 Gd+ lesion count for the Baseline Period
- Mean T1 Gd+ lesion count for the Baseline Period
  - 0
  - >0
  - Non-evaluable
  - Missing
- T1 Gd+ lesion count at the Screening Visit
- T1 Gd+ lesion count at the Screening Visit
  - 0
  - 1
  - >1
  - Non-evaluable
  - Missing
- T1 Gd+ lesion count at the Baseline Visit
- T1 Gd+ lesion count at the Baseline Visit
  - 0
  - 1
  - >1
  - Non-evaluable
  - Missing
- New T1 Gd+ lesion count at the Baseline Visit
- New T1 Gd+ lesion count at the Baseline Visit
  - 0
  - 1
  - >1
  - Non-evaluable
  - Missing

T1 Gd+ lesion volume:

- T1 Gd+ lesion volume at the Screening Visit
- T1 Gd+ lesion volume at the Baseline Visit

T1-hypointense lesions:

- T1-hypointense lesion count at the Screening Visit
- T1-hypointense lesion count at the Baseline Visit

T1-hypointense lesion volume:

- T1-hypointense lesion volume (cm^3) at the Screening Visit
- T1-hypointense lesion volume (cm^3) at the Baseline Visit

Total T2 lesions:

- Total T2 lesion count at the Screening Visit
- Total T2 lesion count at the Baseline Visit

Total T2 lesion volume:

- Total T2 lesion volume (cm^3) at the Screening Visit
- Total T2 lesion volume (cm^3) at the Baseline Visit

Active T2 lesions:

- Total active T2 lesion count during Baseline Period
- Total active T2 lesion count during Baseline Period
  - 0
  - 1
  - >1 - < 9
  - ≥9
  - Non-evaluable
  - Missing
- Standardized total active T2 lesion count during the Baseline Period
- Annualized total active T2 lesion count during the Baseline Period
- Standardized /Annualized total active T2 lesion count during the Baseline Period
  - 0
  - >0
  - Non-evaluable
  - Missing

- Standardized total active T2 lesion count (without T1 Gd+) for the Baseline Period
- Annualized total active T2 lesion count (without T1 Gd+) for the Baseline Period
- Standardized /Annualized total active T2 lesion count (without T1 Gd+) for the Baseline Period
    - 0
    - >0
    - Non-evaluable
    - Missing

CUA lesions:

- Standardized CUA lesion count for the Baseline Period
- Annualized CUA lesion count for the Baseline Period
- Standardized /Annualized CUA lesion count for the Baseline Period
    - 0
    - >0
    - Non-evaluable
    - Missing

Note: While standardized lesion count is used in the 6-month IA, the annualized lesion count is used in the final analysis.

Vital Signs

The following Baseline characteristics will be provided in summary tables:

- Height, weight, body surface area, body mass index
- Body temperature, heart rate, Systolic Blood Pressure, Diastolic Blood Pressure

The body surface area (BSA) and body mass index (BMI) will be calculated with the following equations:

- $BSA(m^2) = ([height(cm) * weight(kg)] / 3600) ^ 0.5$
- $BMI (kg/m^2) = [weight (kg) / height (cm)^2] * 10000$

12 Previous or Concomitant Medications/Procedures

Concomitant medications are medications, other than study medications, which are taken by subjects during the study.

Concomitant medications will be summarized from the "Concomitant medication" eCRF page. ATC-1st level and preferred term will be tabulated as given from the WHO-DD dictionary current version. In case multiple ATC's are assigned to a drug, all ATC-1st level will be used for reporting. All medications entered into the "Concomitant medication" eCRF page will be assumed to be "concomitant" irrespective of the actual start and end dates. In addition, all concomitant medications as well as concomitant medications given for disease related conditions will be presented by PT and by decreasing frequency.

Relevant previous medications are medications, other than study medications, which stopped before enrolment (i.e. date of informed consent [IC]). DMDs (see Section 8.2) administered between IC and start of study medication are major PDs that will be reported as relevant previous medications as well.

Relevant previous medications will be summarized from the "Relevant previous medication details" eCRF page. ATC-1st level and preferred term will be tabulated as given from the WHO-DD dictionary current version. In case multiple ATC's are assigned to a drug, all ATC-1st level will be used for reporting. All medications entered into the "Relevant previous medication details" eCRF page will be assumed to be "previous" irrespective of the actual start and end dates. In addition, all relevant previous medications and relevant previous medications given for disease related conditions will be presented by PT and decreasing frequency.

All relevant previous medications which are classified as DMDs will be presented by PT. DMDs which are taken within 6 months prior to start of study medication (i.e. DMD end date ≥ start of study medication – 182.625) will be presented by PT. The length of the washout Period (start of study medication - DMD end date + 1) of the last DMD within 6 months prior to start of study medication will be summarized. The last DMD will be defined as the DMD with the latest stop date. If the DMD end date is partially missing, the day will be imputed by the 15th of the month but the date will be truncated to IC date -1 if the imputation results in a later date. If the month is missing as well or the date is completely missing the end date will not be replaced and it assumed that the DMD stopped earlier than 6 months prior to start of study medication.

Concomitant procedures which were undertaken any time on study will be listed by subject for the SAF.

13 Treatment Compliance and Exposure

Two years of treatment are planned in this study. Subjects will take tablets in Week 1 (Treatment week 1) and Week 5 (Treatment week 2) of each year. All dosing calculations and summaries will be based on "Treatment Administration" and "Treatment Termination" eCRFs pages.

The following summary tables will be provided for the SAF:

- Duration of therapy,
- Compliance and Drug Accountability

The duration will be presented for Treatment Course 1 Treatment Period, Treatment Course 2 Treatment Period and the Treatment Period in days.

- Duration (days)= (date of last tablet in Period – date of first tablet in Period + 1)

Counts of tablets and compliance will be calculated first for each treatment week:

- Compliance (%) = 100 * number of tablets taken during the treatment week/ number of planned tablets for the treatment week

  If a subject discontinued the treatment before the start of the respective treatment week, compliance will not be derived for this week. If the subject did not take any tablet during the respective treatment week, but had not discontinued the treatment before, compliance will be 0. If the subject was treated during the respective treatment week, but the number of tablets is unknown, compliance will be missing.

Compliance for each year (course) and total will be calculated for all subjects that started the respective treatment period (i.e. taken at least one tablet) as an average of available records obtained for the corresponding treatment weeks. That means, treatment weeks after the subject's treatment discontinuation are not included in the derivation, records of 0 compliance for the corresponding treatment weeks are included in the derivation as such, and missing records result in missing compliance for the respective treatment period.

In addition, compliance will be categorized as follows:

- < 60%
- [60%-80%[
- [80%-90%[
- [90%-110%]
- >110%

The number of planned tablets is based on the weight at the beginning of each treatment course (Table 2).

Table 2: Dose of Mavenclad® per treatment week by subject weight in each treatment year

Weight range	Dose in mg (number tablets) per treatment week	
	Treatment week 1	Treatment week 5
40 to <50	40 mg (4 tablets)	40 mg (4 tablets)
50 to <60	50 mg (5 tablets)	50 mg (5 tablets)
60 to <70	60 mg (6 tablets)	60 mg (6 tablets)
70 to <80	70 mg (7 tablets)	70 mg (7 tablets)
80 to <90	80 mg (8 tablets)	70 mg (7 tablets)
90 to <100	90 mg (9 tablets)	80 mg (8 tablets)
100 to <110	100 mg (10 tablets)	90 mg (9 tablets)
110 and above	100 mg (10 tablets)	100 mg (10 tablets)

The number of subjects with the same planned dosing schema in both Treatments Courses and a different planned dosing schema (i.e. subjects exchanged weight range as defined in the table above) in Treatment Course 2 will be presented for all subjects, who have started Treatment Course 2 (i.e. taken at least one tablet in Treatment Course 2).

The time difference between the start of the Treatment Course 1 Treatment Period and the start of the Treatment Course 2 Treatment Period will be calculated as follows:

- Relative Start of Treatment Course 2 (days) = Start of Treatment Course 2 - Start of Treatment Course 1 + 1.

The Relative Start of Treatment Course 2 will be presented together with the number of subjects in the following groups for the SAF:

- Treatment Course 2 not started,
    - and discontinued before the Month 12 Visit,
    - and discontinued at or after Month 12 Visit
        - Lymphocyte count < 800 cells/mm³ at Month 12 Visit,
        - Reason potentially related to COVID-19
- Treatment Course 2 started,
    - and not delayed (see Section 9 for definition),
    - and delayed,
        - and any Lymphocyte count < 800 cells/mm³ at or after Month 12 Visit and before start of Treatment Course 2.
    - Before or at / after Start of COVID-19 pandemic

The cumulative dose is defined as the sum of the number of tablets taken 10 mg divided by the weight for treatment year:

Cumulative dose = number of tablets taken in Treatment Course 1 * 10mg / weight in kg at Baseline + number of tablets taken in Treatment Course 2 * 10mg / weight in kg at Month 12b Visit.

The cumulative dose will be calculated only if the weight and number of tablets are available. Otherwise it will be missing. If the Treatment Course 2 wasn't started (i.e. no tablet taken in Treatment Course 2), the cumulative dose will be calculated only for the Treatment Course 1.

A subject data listing of the treatment compliance will be provided for the SAF.

14 Efficacy Analyses

The following sections describe the planned analyses for each of efficacy endpoints.

For the detailed definition of covariates and stratification factors that are used in the statistical models see Section 9. Details about the derived MRI endpoints and general handling of MRI data is described in Section 9 ("Data Handling of MRI data").

Descriptive summary statistics will be presented for the absolute values and the changes from Baseline as applicable by Visit [Protocol Scheduled Visits except for Baseline (defined in Section 9)], or Period, for all efficacy endpoints (and the components, where applicable) for the FAS and respective subgroups or subsets for which the variables are analyzed. Details about the presentation of continuous and categorical variables are given in Section 9.

Wherever possible, all estimated results from the statistical models will be calculated with the same observed margin which reflects the population of the whole corresponding analysis set, regardless of missing data.

14.1 Primary Endpoints: Differences in the counts of CUA MRI lesions during the first 6 months compared to Baseline

The primary endpoints for the trial are defined as the differences in counts of CUA MRI lesions during the first 6 months compared to Baseline, i.e., the following differences will be evaluated:

1. Period of Month 1 to Month 6 compared to the Baseline Period.
2. Period of Month 2 to Month 6 compared to the Baseline Period,
3. Period of Month 3 to Month 6 compared to the Baseline Period,

For the detailed definition of Periods, please see Section 9 "Data Handling of MRI data".

14.1.1 Primary Objective: Analysis of primary endpoints

The differences in counts of CUA lesions will be evaluated using a mixed-effects linear model, accounting for within-center/region correlation through a hierarchical model. The analysis will adjust for Baseline factors deemed to be prognostic for the primary endpoint, as judged by clinical experts:

- CUA lesion count during the Baseline Period,
- Age,
- EDSS at Baseline (≤3/>3).

The results of the mixed-effects linear model will be used to describe the effect size. A review of Baseline data has shown that the distribution of the primary endpoint data does not follow Normal distribution. Consequently, the hypotheses will be tested by a Wilcoxon signed-rank test which employs ranks of absolute differences from Baseline for each testing Period (i.e., p_1, p_2, and p_3) using average ranks for tied values.

The analysis will also adjust for the difference in length and number of MRIs of the Periods to be compared (see Section 9 "Data Handling of MRI data" for details of lesion count standardization).

The difference in the counts of CUA lesions during the three Periods compared to the Baseline Period will be tested in a sequential order. The three hypotheses are defined as follows:

$$H_{0i}: \Delta\,\mathrm{CUA}(p_i) \geq 0 \quad \text{vs.} \quad \Delta\,\mathrm{CUA}(p_i) < 0, \qquad i = 1,2,3$$

$$\Leftrightarrow H_{0i}: \#\mathrm{CUA}(p_i) \geq \#\mathrm{CUA}(p_0) \text{ vs. } \#\mathrm{CUA}(p_i) < \#\mathrm{CUA}(p_0), \qquad i = 1,2,3$$

with

$$\Delta\mathrm{CUA}(p_i) = \#\mathrm{CUA}(p_i) - \#\mathrm{CUA}(p_0), \qquad i = 1,2,3,$$

$\#\mathrm{CUA}(p_i)$: standardized CUA lesion count during Period p_i, $\quad i = 0,1,2,3,$

p_0: Baseline Period (Period from Screening to Baseline),

p_i: Period Month i to Month 6, $\quad i = 1,2,3.$

The sequential testing procedure will start with Period p_3, followed by Period p_2 and p_1, i.e., the hypotheses will be tested in the following order:

1. H_{03}
2. H_{02}
3. H_{01}

The three hypotheses will be tested one-sided on a 2.5% significance level. The testing procedure will stop as soon as one of the hypotheses cannot be rejected following the pre-specified order. Due to this sequential order of tests an adjustment for a potential type-I-error inflation due to the multiple testing is not required.

An estimate for the difference in CUA lesions during the specified Periods compared to the Baseline Period will be reported, together with one-sided p-values. In addition, 95% CI and 2-sided p-values will be presented to allow for comparison with the 2-sided secondary and tertiary analyses.

The LS Means will be calculated with observed margin which reflects the distribution of age, EDSS categories at Baseline and respective Baseline Period CUA Lesion of the FAS. An unstructured covariance matrix will be assumed for the model. If the model doesn't converge a variance components covariance structure will be used instead or the results of sensitivity analysis with center effect as a fixed effect will be used instead.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoints: Differences in the counts of CUA MRI lesions during the first 6 months (i.e., during Periods months 1-6, 2-6, 3-6) compared to Baseline (i.e., the Period from Screening to Baseline) [(a)]			
Primary (FAS)	1. Period 3 (Month 3-6): $\Delta CUA(p_3)$ (Hypothesis 3) 2. Period 2 (Month 2-6): $\Delta CUA(p_2)$ (Hypothesis 2) 3. Period 1 (Month 1-6): $\Delta CUA(p_1)$ (Hypothesis 1)	P-values for the three Hypotheses from the Wilcoxon signed-rank test will be presented. The testing procedure will stop as soon as one of the hypotheses cannot be rejected following the pre-specified order (H3, H2, H1). Due to this sequential order of tests an adjustment for a potential type-I-error inflation due to the multiple testing is not required. The Wilcoxon signed-rank test will be complemented by the estimated Least Square Means (LS Means) and corresponding Standard Errors (SE) including one-sided p-values as well as two-sided p-value and 95% Cis from the mixed-effects linear model with the following adjusting factors: • Baseline score, • Age (in years), • EDSS at Baseline (≤3, >3), • Within-pooled center correlation. In addition, the distribution of $CUA(p_i)$ and $\Delta CUA(p_i)$ will be displayed graphically using box plots.	Missing observations: Subjects with a missing CUA lesion count at either the Baseline Period or the respective post-Baseline Period will not be included in the analysis.
$\Delta CUA(p_i)$ = Difference in the standardized CUA lesion count between Period i and the Baseline Period (a) 6-month interim analysis			

14.1.2 Primary Objective: Sensitivity Analyses of the primary endpoints

The robustness of the results of the primary analysis will be evaluated by the following

- Multiple Imputation to handle missing data using different assumptions,
- Non-parametric factorial model for longitudinal data,
- Generalized model assuming negative binomial distribution,
- Mixed-effects linear model with pooled-centers as fixed effects.

To evaluate further the impact of the potential zero inflation, the primary endpoint will be classified in different response categories for each Period as follows:

- Presence of MRI activity
    - Yes (CUA lesion count > 0)
    - No (CUA lesion count = 0)
- Standardized CUA lesion count classified to:
    - 0 (standardized CUA lesion count = 0)
    - >0 – 1 (standardized CUA lesion count > 0 and less or equal to 1)
    - >1 (standardized CUA lesion count > 1)

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoints: Differences in the counts of CUA MRI lesions during the first 6 months (i.e., during Periods months 1-6, 2-6, 3-6) compared to Baseline Period (i.e., the Period from Screening to Baseline) [a].			
Sensitivity (FAS by subgroup "High-relapse activity")	Period 3 (Month 3-6): $\Delta CUA(p_3)$ Period 2 (Month 2-6): $\Delta CUA(p_2)$ Period 1 (Month 1-6): $\Delta CUA(p_1)$	Same as in the Primary Analysis (see Section 14.1.1)	Same as in the Primary Analysis (see Section 14.1.1)
Sensitivity (FAS by subgroup "Previous treatment with DMDs")	Period 3 (Month 3-6): $\Delta CUA(p_3)$ Period 2 (Month 2-6): $\Delta CUA(p_2)$ Period 1 (Month 1-6): $\Delta CUA(p_1)$		
Sensitivity (FAS for subset "Baseline Period CUA count > 0")	Period 3 (Month 3-6): $\Delta CUA(p_3)$ Period 2 (Month 2-6): $\Delta CUA(p_2)$ Period 1 (Month 1-6): $\Delta CUA(p_1)$		
Sensitivity (FAS)	Period 3 (Month 3-6): $\Delta CUA(p_3)$ Period 2 (Month 2-6): $\Delta CUA(p_2)$ Period 1 (Month 1-6): $\Delta CUA(p_1)$	Same as in the Primary Analysis (see Section 14.1.1)	Multiple Imputation (see below for details)
Sensitivity (FAS)	Period 3 (Month 3-6): $\Delta CUA(p_3)$ Period 2 (Month 2-6): $\Delta CUA(p_2)$ Period 1 (Month 1-6): $\Delta CUA(p_1)$	Non-parametric factorial model for longitudinal data. Fixed factors: • Age in years (≤ 40,40 - < 65), • EDSS at Baseline (≤3, >3), (see below for details)	Same as in the Primary Analysis (see Section 14.1.1).
Sensitivity (FAS)	Period 3 (Month 3-6): $\#CUA(p_3)/\#CUA(p_0)$ Period 2 (Month 2-6): $\#CUA(p_2)/\#CUA(p_0)$ Period 1 (Month 1-6): $\#CUA(p_2)/\#CUA(p_0)$	Generalized model assuming a negative binomial distribution with the following adjusting factors: • Period • Age (in years), • EDSS at Baseline (≤3, >3), • Within-pooled center correlations. Estimated standardized CUA for the Periods as well as the ratios of each post-Baseline Period versus the Baseline Period, and corresponding Standard Errors (SE) will be presented including estimated fixed effects including the SE, 2-sided p-values and 95% CI	Same as in the Primary Analysis (see Section 14.1.1).

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Sensitivity (FAS)	Period 3 (Month 3-6): $\Delta CUA(p_3)$ Period 2 (Month 2-6): $\Delta CUA(p_2)$ Period 1 (Month 1-6): $\Delta CUA(p_1)$	Mixed-effects linear model with the following adjusting factors: • Baseline score, • Age (years), • EDSS at Baseline (≤3, >3), • Period, • pooled center. Estimated Least Square Means (LS Means) and corresponding Standard Errors (SE) will be presented by Visit including 2-sided p-values and 95% CI.	Same as in the Primary Analysis (see Section 14.1.1).
Categorization of the Primary Endpoints: Presence of MRI activity (at least one CUA lesion) during the first 6 months (i.e., during Periods 1-3 compared to Baseline Period (i.e., the Period from Screening to Baseline)[(a)].			
Sensitivity (FAS) Sensitivity (FAS by subgroup High-relapse activity) Sensitivity (FAS by subgroup "Previous treatment with DMDs")	Cross-tabulation for each Period i, where i=1,2,3 • No: #CUA(p_i) = 0 • Yes: #CUA(p_i) > 0 vs Baseline Period: • No: #CUA(p_0) = 0 • Yes: #CUA(p_0) >0	McNemar Test.	Same as in the Primary Analysis (see Section 14.1.1).

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Categorization of the Primary Endpoints: Classified CUA lesion count during the first 6 months (i.e., during Periods 1-3) compared to Baseline Period (i.e., the Period from Screening to Baseline)[a].			
Sensitivity (FAS)	Cross-tabulation for each Period i, where i=1,2,3 • 0: #CUA(p_i) = 0 • >0-1: 0 < #CUA(p_i) ≤ 1 • >1: #CUA(p_i) > 1 vs Baseline Period: • 0: #CUA(p_0) = 0 • >0-1: 0 < #CUA(p_0) ≤ 1 • >1: #CUA(p_0) >1	Bowker's test of symmetry.	Same as in the Primary Analysis (see Section 14.1.1).
Sensitivity (FAS by subgroup "High-relapse activity")			
Sensitivity (FAS by subgroup "Previous treatment with DMDs")			
ΔCUA(p_i) = Difference in the standardized CUA lesion count between Period i and the Baseline Period, i=1 (Month1-6), 2 (Month 2-6), 3 (Month 3-6) #CUA(p_i) = Standardized CUA lesion count during Period i, i=0 (Baseline Period), 1 (Month1-6), 2 (Month 2-6), 3 (Month 3-6) (a) 6-month interim analysis			

Multiple imputation

In order to evaluate the robustness of the assumption applied in the primary analysis that missing data are observed as missing at random (MAR), the primary analysis will be repeated applying a pattern mixture model. If missingness can be considered MAR (e.g. MRI missing for technical reasons), data will be imputed by multiple imputation from post-Baseline data while if it is considered as missing not at random (MNAR) (e.g. drop-out due to lack of efficacy), data will be imputed from Baseline data.

The multiple imputation procedure will use a pre-specified seed number repeating the imputation procedure 100 times.

The following reasons for missing MRI results will be considered as MAR:

- MRI classified as non-evaluable by the central MRI reading
- MRI missing at Baseline
- Subject discontinued the study before the Month 6 Visit with primary reason
    - Lost to follow-up
    - Any Protocol non-compliance reported as "Other" and classified as non-related to study treatment
    - Any withdrawal of consent classified as non-related to study treatment
    - Any pregnancy (Discontinuation Reason "Adverse Event" and "Pregnancy" reported as AE leading to discontinuation.
    - Any "Other" reason classified as non-related to study treatment

All other missing MRI results will be handled as MNAR.

The following procedure for the different types of missing data will be performed:

- CUA lesion counts missing at the Baseline Period will be imputed from the distribution of available CUA lesion counts at the Baseline Period.
- CUA lesion counts missing at any post-Baseline Period that are considered MAR will be imputed from the distribution of available CUA lesion counts of the same post-Baseline Period.
- CUA lesion counts missing at any post-Baseline Period that are considered MNAR will be imputed from the distribution of CUA lesion counts of the Baseline Period

The changes from the Baseline Period will be calculated for all Periods and subjects, and the primary analysis (i.e. the Wilcoxon test as well as the mixed-effects linear model) will be repeated for each of the imputation repetition (i.e. for each of the imputed datasets).

Results combined using Rubin's rule [5] will be presented.

Non-parametric factorial model

The primary analysis will be repeated using a factorial model for longitudinal data according to Brunner, Domhoff and Langer [2] (2002). Following the authors' terminology, a Fx-LD-F1 model will be assumed with x=2 fixed factors (age, EDSS at Baseline) and one longitudinal factor ('LD') which is reflecting Baseline and one of the primary post-Baseline Periods.

The underlying nonparametric hypothesis is defined in terms of the distribution functions. In a simple model with two time points and no fixed factors one would assume that the pairs of lesion count data (Baseline, post Baseline) would have marginal distributions F_s, s=1, 2, and the null hypothesis would be H_0: $F_1 = F_2$, the alternative accordingly H_0: $F_1 \neq F_2$. In a simple shift model one would assume that these marginal distribution functions only differ through a 'location parameter' μ, namely one would assume that $F_2(x) = F_1(x-\mu)$ and the null hypothesis would be $\mu=0$. For multiple fixed factors and one 'LD' factor the notation of hypotheses is more complicated and can be found in Brunner, Domhoff and Langer [2] (2002) in section 8.3 and especially in 8.3.1 for the null hypothesis of 'no time effect'.

Midranks over all CUA lesions from the Baseline Period and respective post-Baseline Period will be calculated. The ranks will be analyzed with a heteroscedastic factorial designs model with repeated measures (Baseline and one post-Baseline Period) and unspecified covariance matrices. The following factors will be used:

- Age groups (≤ 40,>40),
- EDSS at Baseline (≤3/>3).

The p-value for the time effect will be calculated as described by Brunner, Domhoff and Langer [2] (2002).

Generalized linear model assuming negative binomial distribution

The standardized CUA lesion count will be evaluated using a generalized mixed-effects linear model with log link function. Period (i.e Baseline Period, each post-Baseline Period i, i=1,2,3) will be analyzed as a repeated factor accounting for within subject and within-center/region correlation using an unstructured covariance matrix. Age and EDSS at Baseline (≤3, >3) will be used as fixed effect covariates.

The ratio of the standardized CUA lesion count of each post-Baseline Period versus the Baseline Period will be calculated as the inverse log of the difference of the estimated contrast between each post-Baseline Period and the Baseline Period.

The CUA lesions are already standardized for the observation time and therefore no offset will be used. The estimated standardized CUA lesion count will be calculated based on the observed margin of the FAS at Baseline.

The estimates, standard deviation and 95% confidence intervals for the standardized CUA lesion count at each Period and the ratio between Periods will be presented together with the estimated fixed effects.

If the model doesn't converge a variance components covariance structure will be used instead of the unstructured covariance matrix.

14.2 Secondary Endpoints: Characterization of immune cell subsets count at the end of 3, 6, 12, 15, 18 and 24 months compared to Baseline

List of biomarker parameters per each panel is presented in Appendix 3. (Further, detailed information can be found in the corresponding DTA [9] and Parameter Mapping specification [10]).

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary endpoint: Change of immune cell subset counts from Baseline to Month 3, 6, 12, 15, 18 and 24 Visits			
Secondary (FAS)	Change from Baseline in each immune cell subset count at Month i Visit, where i= 3, 6, 12, 15, 18 and 24.	• Descriptive summary statistics including percentage change. • Number of subjects with a value below LLOQ together with the LLOQ limit, if available. • Number of subjects with a value outside reference range (i.e. below lower limit or above upper limit of normal) with the reference range, if available. • 95% confidence intervals of the mean • Wilcoxon signed-rank test with the associate p-value • Box/scatter/time series plots.	If cell count is missing for a Visit but the re-test is available, the value from the re-test will be used. Otherwise, the post-Baseline re-test results will be ignored for all analyses by Visit.

Handling of values below Lower Limit of Quantification (LLOQ):

Immune cell subsets reported as below the LLOQ will be imputed as follows:

- If the LLOQ is available then half of the LLOQ will be imputed,
- Otherwise, a zero will be imputed.

14.3 Tertiary Endpoints

14.3.1 Changes in CUA lesion count

The changes in CUA lesion counts from the Baseline Period to the post-Baseline Periods are defined in the Section 9 "Definition of Study Periods" and "Data Handling of MRI data".

CUA lesion counts will further be classified for each Period as follows:

- CUA lesion count > 0
    - Yes (CUA lesion count > 0)
    - No (CUA lesion count = 0)

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoints: Change from the Baseline Period in Annualized CUA lesion count to the six months post-Baseline Periods			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 6.1 (Baseline-Month 6): $\Delta CUA(p_{6.1})$ Period 6.2 (Month 6-12): $\Delta CUA(p_{6.2})$ Period 6.3 (Month 12-18): $\Delta CUA(p_{6.3})$ Period 6.4 (Month 18-24): $\Delta CUA(p_{6.4})$	Mixed-effects linear model for repeated measures with the following adjusting factors: • Baseline score, • Age (years), • EDSS at Baseline (≤3, > 3), • Period, • Pooled center • Within-subject correlation. Estimated Least Square Means (LS Means) and corresponding Standard Errors (SE) will be presented by Period including 2-sided p-values and 95% CI.	Missing observations at Baseline: Subjects with a missing Baseline score will not be included in the linear model. Missing post-Baseline observations: Missing post-Baseline assessments will not be imputed. The repeated measurement model handles missing post-Baseline assessments under the assumption of MAR.
Tertiary endpoints: Ratio of the six months post-Baseline Periods versus the Baseline Period in Annualized CUA lesion count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 6.1 (Baseline-Month 6): $\#CUA(p_{6.1})/\#CUA(p_0)$ Period 6.2 (Month 6-12): $\#CUA(p_{6.2})/\#CUA(p_0)$ Period 6.3 (Month 12-18): $\#CUA(p_{6.3})/\#CUA(p_0)$ Period 64 (Month 18-24): $\#CUA(p_{6.4})/\#CUA(p_0)$	Generalized model assuming a negative binomial distribution with the following adjusting factors: • Age (years), • EDSS at Baseline (≤3, >3), • Period, • Within-subject correlation. Estimated standardized CUA for the Periods as well as the ratios of each post-Baseline Period versus the Baseline Period, and corresponding Standard Errors (SE) will be presented including estimated fixed effects including the SE, 2-sided p-values and 95% CI	All data available will be used in the model.
Tertiary endpoints: Change from the Baseline Period in Annualized CUA lesion count to the yearly post-Baseline Periods			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs") TCS-1 TCS-2	Period 12.1 (Baseline-Month 12): $\Delta CUA(p_{12.1})$ Period 12.2 (Month 12-24): $\Delta CUA(p_{12.2})$	Mixed-effects linear model for repeated measures as specified above.	Same as above for the mixed effect linear model with repeated measures.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoints: Ratio of the yearly post-Baseline Periods versus the Baseline Period in Annualized CUA lesion count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 12.1 (Baseline-Month 12): #CUA(p12.1)/#CUA(p0) Period 12.2 (Month 12-24): #CUA(p12.2)/#CUA(p0)	Generalized model as specified as above.	Same as above for the generalized model.
Tertiary endpoint: Change from the Baseline Period in Annualized CUA lesion count to the 2-year post-Baseline Period			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 24.1 (Baseline-Month 24): ΔCUA(p24.1)	Mixed-effects linear model with the following adjusting factors: • Baseline score, • Age (years), • EDSS at Baseline (≤3, > 3), • Pooled center Estimated Least Square Means (LS Means) and corresponding Standard Errors (SE) will be presented including 2-sided p-values and 95% CI.	Same as in the Primary Analysis (see Section 14.1.1)
Tertiary endpoints: Ratio of the 2-year post-Baseline Period versus the Baseline Period in Annualized CUA lesion count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 24.1 (Baseline-Month24): #CUA(p24.1)/#CUA(p0)	Generalized model assuming a negative binomial distribution with the following adjusting factors: • Age (years), • EDSS at Baseline (≤3, >3), Estimated standardized CUA for the Periods as well as the ratios of the post-Baseline Period versus the Baseline Period, and corresponding Standard Errors (SE) will be presented including estimated fixed effects including the SE, 2-sided p-values and 95% CI.	Same as above for the generalized model.
Tertiary endpoints: Change from the Baseline Period in Annualized CUA lesion count to the yearly post-Baseline Periods excluding the first month			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 11.1 (Month 1-12): ΔCUA(p11.1) Period 11.2 (Month 1-24): ΔCUA(p11.2)	Mixed-effects linear model as specified above.	Same as in the Primary Analysis (see Section 14.1.1).

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoints: Ratio of the yearly post-Baseline Periods excluding the first month versus the Baseline Period in Annualized CUA lesion count			
Tertiary (FAS)	Period 11.1 (Month 1-12): ΔCUA(p11.1)	Generalized model as specified above.	Same as above for the generalized model.
Tertiary (FAS by subgroup "High-relapse activity")	Period 11.2 (Month 1-24): ΔCUA(p11.2)		
Tertiary (FAS by subgroup "Previous treatment with DMDs")			
Tertiary endpoint: Change from Baseline in Annualized CUA lesion count by Visit			
Tertiary (FAS)	Change from Baseline in CUA lesion count at Month i Visit, where i= 1, 2, 3, 6, 12, 15, 18 and 24.	Mixed-effects linear model for repeated measures with the following adjusting factors: • Baseline score, • Age (years), • EDSS at Baseline (≤3, > 3), • Visit[$], • Time between scans (years), • Pooled center, • Within-subject correlation. Estimated Least Square Means (LS Means) and corresponding Standard Errors (SE) will be presented by Visit including 2-sided p-values and 95% CI.	Same as above for mixed effect linear model with repeated measures.
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs")			
Tertiary Endpoint: CUA lesion count > 0			
Tertiary (FAS)	Cross-tabulation for each post-Baseline Period: • No: #CUA($p_{post\text{-}Baseline}$)= 0 • Yes: #CUA($p_{post\text{-}Baseline}$) > 0 vs Baseline Period: • No: #CUA(p_0) = 0 • Yes: #CUA(p_0)>0	McNemar Test.	Missing observations at Baseline: Subjects with a missing Baseline score will not be included in McNemar Test, however separate cross-tabulation table including missing/not-evaluable lesions counts will be presented and thus providing percentage related to all subjects. Missing post-Baseline observations: Same as above but adapted for missing post-Baseline observations (see "Missing observations at Baseline").
Tertiary (FAS by subgroup High-relapse activity)			
Tertiary (FAS by subgroup "Previous treatment with DMDs")			
ΔCUA= Difference in the annualized CUA lesion count between post-Baseline Periods and the Baseline Period #CUA= Annualized CUA lesion count during Periods			

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
p_0= Baseline Period $=Sequential Visit Periods			

Mixed-effects linear model for repeated measures

The change from Baseline in the annualized CUA lesion count by Period or Visit (i.e. the Sequential Visit Period) will be analyzed by a repeated mixed-effects linear model, which adjusts for the Baseline score (i.e. the annualized count), age (in years), EDSS at Baseline (≤3, >3), pooled center, Period /or Visit, within subject correlation and time between scans (in years), where applicable. An unstructured covariance matrix will be assumed for the model. If the model doesn't converge an alternative covariance structure will be used instead.

The estimated annualized CUA lesion count will be calculated based on the observed margin of the corresponding analysis set at Baseline.

Mixed-effects linear model

The change from Baseline in annualized CUA lesion count for each Period separately will be analyzed by a mixed-effects linear model, which adjusts for the Baseline score (i.e., the annualized count), age (in years), EDSS at Baseline (≤3, >3), pooled center, time between scans (in years) and within subject correlation. An unstructured covariance matrix will be assumed for the model. If the model doesn't converge an alternative covariance structure will be used instead.

The estimated annualized CUA lesion count will be calculated based on the observed margin of the corresponding analysis set at Baseline.

Generalized linear model assuming negative binomial distribution

The annualized CUA lesion count will be evaluated using a generalized mixed-effects linear model with log link function assuming a negative binomial distribution. Period (i.e. Baseline Period, each post-Baseline Period as specified above) will be analyzed as: a) a repeated factor accounting for time between scans (in years) if the time is different between scans, or b) neglected, if the time between scans is constant (for example: for every 6 months Periods, 1 yearly Periods); and within subject correlation using an unstructured covariance matrix. Age and EDSS at Baseline (≤3, >3) will be used as fixed effect covariates.

The ratio of the annualized CUA lesion count of each post-Baseline Period versus the Baseline Period will be calculated as the inverse log of the difference of the estimated contrast between each post-Baseline Period and the Baseline Period.

Offset will be applied if needed.

The estimates, standard deviation and 95% confidence intervals for the annualized CUA lesion count at each Period and the ratio between Periods will be presented together with the estimated fixed effects. If the model doesn't converge an alternative covariance structure will be used instead of the unstructured covariance matrix.

The estimated annualized CUA lesion count will be calculated based on the observed margin of the corresponding analysis set at Baseline.

14.3.2 CUA lesion count

CUA lesion counts for the Sequential Visit Periods are defined in the Section 9 "Definition of Study Periods" and "Data Handling of MRI data".

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Annualized CUA lesion count by Visit			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Absolute CUA lesion count at Month i Visit, where i= 0, 1, 2, 3, 6, 12, 15, 18 and 24.	Mixed-effects linear model for repeated measures for the absolute values over 24 months with the following adjusting factors: • Baseline score, • Age (in years), • EDSS at Baseline (≤3, > 3), • Visit[$], • Time between scans (years), • Pooled center, • Within-subject correlation. Estimated Least Square Means (LS Means) and corresponding Standard Errors (SE) will be presented by Visit including 95% CI.	Same as for mixed effect linear model with repeated measures in Section 14.3.1
$=Sequential Visit Periods			

Mixed-effects linear model for repeated measures

As defined in Section 14.3.1 applying adaptations to the endpoints, factors and covariates listed in the table above.

14.3.3 T1 Gd+ lesion count

T1 GD+ lesion counts by Visit and Period are defined in Section 9 "Definition of Study Periods" and "Data Handling of MRI data".

To evaluate further the course of T1 GD+ lesion appearance over time, T1 Gd+ lesions will be further classified as follows for each Visit:

- T1 Gd+ lesion count > 0
    - Yes (T1 Gd+ lesion count > 0)
    - No (T1 Gd+ lesion count = 0)

Analogously for new T1 Gd+ lesion count.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoints: Change from the Baseline Period in T1 Gd+ lesion count to the six months post-Baseline Periods			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 6.1 (Baseline-Month 6): $\Delta T1(p_{6.1})$ Period 6.2 (Month 6-12): $\Delta T1(p_{6.2})$ Period 6.3 (Month 12-18): $\Delta T1(p_{6.3})$ Period 6.4 (Month 18-24): $\Delta T1(p_{6.4})$	Mixed-effects linear model for repeated measures, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)
Tertiary endpoints: Ratio of the six months post-Baseline Periods versus the Baseline Period in T1 Gd+ lesion count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 6.1 (Baseline-Month 6): $\#T1(p_{6.1})/\#T1(p_0)$ Period 6.2 (Month 6-12): $\#T1(p_{6.2})/\#T1(p_0)$ Period 6.3 (Month 12-18): $\#T1(p_{6.3})/\#T1(p_0)$ Period 64 (Month 18-24): $\#T1(p_{6.4})/\#T1(p_0)$	Generalized model assuming a negative binomial, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)
Tertiary endpoints: Change from the Baseline Period in T1 Gd+ lesion count to the yearly post-Baseline Periods			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 12.1 (Baseline-Month 12): $\Delta T1(p_{12.1})$ Period 12.2 (Month 12-24): $\Delta T1(p_{12.2})$	Mixed-effects linear model for repeated measures as specified above.	Same as above for the mixed effect linear model with repeated measures.
Tertiary endpoints: Ratio of the yearly post-Baseline Periods versus the Baseline Period in T1 Gd+ lesion count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 12.1 (Baseline-Month 12): #T1(p12.1)/#T1(p0) Period 12.2 (Month 12-24): #T1(p12.2)/#T1(p0)	Generalized model as specified as above.	Same as above for the generalized model.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Change from the Baseline Period in T1 Gd+ lesion count to the 2-year post-Baseline Period			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 24.1 (Baseline-Month 24): ΔT1(p24.1)	Mixed-effects linear model same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)
Tertiary endpoints: Ratio of the 2-year post-Baseline Period versus the Baseline Period in T1 Gd+ lesion count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 24.1 (Baseline-Month24): #T1(p24.1)/ #T1(p0)	Generalized model assuming a negative binomial distribution with the following adjusting factors: • Age (years), • EDSS at Baseline (≤3, >3), Estimated T1 Gd+ lesions count for the Periods as well as the ratios of the post-Baseline Period versus the Baseline Period, and corresponding Standard Errors (SE) will be presented including estimated fixed effects including the SE, 2-sided p-values and 95% CI.	Same as above for the generalized model.
Tertiary endpoint: Change from Baseline in T1 Gd+ lesion count by Visit			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Change from Baseline in T1 Gd+ lesion count at Month i Visit, where i= 1, 2, 3, 6, 12, 15, 18 and 24.	Mixed-effects linear model for repeated measures, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)
Tertiary Endpoint: T1 Gd+ lesion count > 0			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Cross-tabulation for each post-Baseline Period • No: #T1($p_{post\text{-}Baseline}$)= 0 • Yes: #T1($p_{post\text{-}Baseline}$)> 0 vs Baseline Period: • No: #T1(p_0) = 0 • Yes: #T1(p_0)>0	McNemar Test.	Same as for McNemar test in Section 14.3.1

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: New T1 Gd+ lesion count			
Tertiary (FAS)	New T1 Gd+ lesion count at Baseline and at the Month i Visit, where i= 1, 2, 3, 6, 12, 15, 18 and 24, as well as at selected post-Baseline Periods, i.e. p12.1, p12.2, p24.	Descriptive summary statistics.	
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs")			
Tertiary endpoint: New T1 Gd+ lesion count > 0			
Tertiary (FAS)	Cross-tabulation for each post-Baseline Period • No: # T1 ($p_{post\text{-}Baseline}$)= 0 • Yes: # T1 ($p_{post\text{-}Baseline}$)> 0 vs Baseline Period: • No: # T1 (p_0) = 0 • Yes: # T1 (p_0)>0	Frequency table with percentages,	
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs")			
Tertiary endpoint: Change from Baseline in Mean T1 Gd+ lesion count[(a)]			
Tertiary (FAS)	Period 1 (Month 1-6): $\Delta T1(p_1)$	Same as in the Primary Analysis (see Section 14.1.1)	Same as in the Primary Analysis (see Section 14.1.1)
	Period 2 (Month 2-6): $\Delta T1(p_2)$		
	Period 3 (Month 3-6): $\Delta T1(p_3)$		
$\Delta T1(p_i)$ = Difference in Mean T1 Gd+ lesion count between Period i and the Baseline Period $=Sequential Visit Periods (a) 6-month interim analysis			

Repeated mixed-effects linear model

As defined in Section 14.3.1 applying adaptations to the endpoints, factors and covariates listed in the table above.

Generalized linear model assuming negative binomial distribution:

As defined in Section 14.3.1 applying adaptations to the endpoints, factors and covariates listed in the table above.

14.3.4 T1 Gd+ lesion volume

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Change from Baseline in the T1 Gd+ lesion volume			
Tertiary (FAS)	The absolute volume and change from Baseline to Month i Visit, where i= 1, 2, 3, 6, 12, 15, 18 and 24, in T1 Gd+ lesion volume by Visit	Descriptive summary statistics.	

14.3.5 T1 hypointense lesion count

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Change from Baseline in the T1 hypointense lesion count			
Tertiary (FAS)	The absolute count and change from Baseline to Month i Visit, where i= 1, 2, 3, 6, 12, 15, 18 and 24, in T1 hypointense lesion count by Visit	Descriptive summary statistics.	

14.3.6 T1 hypointense lesion volume

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Change from Baseline in the T1 hypointense lesion volume			
Tertiary (FAS)	The absolute volume and change from Baseline to Month i Visit, where i= 1, 2, 3, 6, 12, 15, 18 and 24, in T1 hypointense lesion volume by Visit	Descriptive summary statistics.	

14.3.7 Active T2 lesion count

The number and changes from Baseline of the different types of active T2 lesions will be presented by Period or Visit.

Active T2 lesion count will be further classified as follows for each Visit:

- Active T2 lesion count > 0
    - Yes (Active T2 lesion count > 0)
    - No (Active T2 lesion count = 0)

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Changes in the standardized total active T2 lesion count (without T1 Gd+) during pre-defined post-Baseline Periods compared to the Baseline Period[(a)]			
Tertiary (FAS)	Change from Baseline of the standardized total active T2 lesion count without T1 Gd+ to Periods 1-3.	Descriptive summary statistics.	
Tertiary endpoint: Changes in standardized total active T2 lesion count during pre-defined post-Baseline Periods compared to the Baseline Period (i.e., the Period from Screening to Baseline)[(a)]			
Tertiary (FAS)	Period 3 (Month 3-6): ΔT2(p3)	Same as in the Primary Analysis (see Section 14.1.1)	Same as in the Primary Analysis (see Section 14.1.1)
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs	Period 2 (Month 2-6): ΔT2(p2)		
Tertiary (FAS for subset "Baseline Period CUA count > 0")	Period 1 (Month 1-6): ΔT2(p1)		
Tertiary endpoint: Total active T2 Lesion count by Visit[(a)]			
Tertiary (FAS)	Change from Baseline in total active T2 Lesion count at Month i Visit, where i=2, 3, 6.	Same as in the Tertiary Analysis of Change from Baseline in T1 Gd+ lesion count (see Section 14.3.3)	Same as in the Tertiary Analysis of Change from Baseline in T1 Gd+ lesion count (see Section 14.3.3)
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs			
Tertiary (FAS for subset "Baseline Period CUA count > 0")			
Tertiary endpoints: Change from the Baseline Period in Annualized Active T2 lesion count to the six months post-Baseline Periods			
Tertiary (FAS)	Period 6.1 (Baseline-Month 6): $\Delta T2(p_{6.1})$ Period 6.2 (Month 6-12): $\Delta T2(p_{6.2})$ Period 6.3 (Month 12-18): $\Delta T2(p_{6.3})$ Period 6.4 (Month 18-24): $\Delta T2(p_{6.4})$	Mixed-effects linear model for repeated measures, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs")			

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoints: Ratio of the six months post-Baseline Periods versus the Baseline Period in Annualized Active T2 lesion count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 6.1 (Baseline-Month 6): #T2($p_{6.1}$)/#T2(p_0) Period 6.2 (Month 6-12): #T2($p_{6.2}$)/#T2(p_0) Period 6.3 (Month 12-18): #T2($p_{6.3}$)/#T2(p_0) Period 64 (Month 18-24): #T2($p_{6.4}$)/#T2(p_0)	Generalized model assuming a negative binomial, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)
Tertiary endpoints: Change from the Baseline Period in Annualized Active T2 lesions count to the yearly post-Baseline Periods			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 12.1 (Baseline-Month 12): $\Delta T2(p_{12.1})$ Period 12.2 (Month 12-24): $\Delta T2(p_{12.2})$	Mixed-effects linear model for repeated measures as specified above.	Same as above for the mixed effect linear model with repeated measures.
Tertiary endpoints: Ratio of the yearly post-Baseline Periods versus the Baseline Period in Annualized Active T2 lesions count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 12.1 (Baseline-Month 12): #T2(p12.1)/#T2(p0) Period 12.2 (Month 12-24): #T2(p12.2)/#T2(p0)	Generalized model as specified as above.	Same as above for the generalized model.
Tertiary endpoint: Change from the Baseline Period in Annualized Active T2 lesions count to the 2-year post-Baseline Period			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 24.1 (Baseline-Month 24): $\Delta T2(p24.1)$	Mixed-effects linear model same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)
Tertiary endpoints: Ratio of the 2-year post-Baseline Period versus the Baseline Period in Annualized Active T2 lesions count			
Tertiary (FAS) Tertiary (FAS by subgroup "High-relapse activity") Tertiary (FAS by subgroup "Previous treatment with DMDs")	Period 24.1 (Baseline-Month24): #T2(p24.1)/ #T2(p0)	Generalized model assuming a negative binomial, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as above for the generalized model.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Change from Baseline in Annualized active T2 Lesion count by Visit			
Tertiary (FAS)	Change from Baseline in active T2 Lesion count at Month i Visit, where i=1, 2, 3, 6, 12, 15, 18 and 24.	Mixed-effects linear model for repeated measures, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs")			
Tertiary endpoint: Active T2 Lesion count > 0			
Tertiary (FAS)	Cross-tabulation for each post-Baseline Visit • No: #T2($p_{post\text{-}Baseline}$)= 0 • Yes: #T2($p_{post\text{-}Baseline}$)> 0 vs Baseline Period: • No: #T2(p_0) = 0 • Yes: #T2(p_0)>0	McNemar Test.	Same as for McNemar test in Section 14.3.1
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs")			
Tertiary endpoint: Change from Baseline in Total T2 Lesion count by Visit			
Tertiary (FAS)	Change from Baseline in Total T2 Lesion count at Month i Visit, where i=1, 2, 3, 6, 12, 15, 18 and 24.	Descriptive summary statistics.	
Tertiary (FAS by subgroup "High-relapse activity")			
Tertiary (FAS by subgroup "Previous treatment with DMDs")			
$\Delta T2(p_i)$ = Difference in the standardized/annualized total active T2 lesion count between Period i and the Baseline Period Further Periods or comparisons may be added by an Amendment to the IAP (a) 6-month interim analysis			

14.3.8 Responder rate during the different Periods

Subjects will be classified as Responder for a post-Baseline Period if the standardized CUA lesion count decreased by at least 1 in 6 months in comparison to the Baseline Period:

- Responder: $\Delta\mathrm{CUA}(p_i) = \left(\#\mathrm{CUA}(\mathrm{p}_i) - \#\mathrm{CUA}(\mathrm{p}_0)\right) * 6 \geq -1,\ i = \text{Period } 1, 2, 3,$
- Non-Responder: otherwise.

Subjects with missing assessments will be classified as "Non-Responder".

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Responder rate during the different post-Baseline Periods [a]			
Tertiary (FAS)	Responder rates for Periods 1-3.	Descriptive summary statistics and 95% confidence intervals	Missing Baseline Period: Subjects with a missing CUA lesion count for the Baseline Period will not be included in analysis. Subjects with a missing post-Baseline Period will be classified as Non-Responder for the respective Period.
(a) 6-month interim analysis			

14.3.9 T2 lesion volume

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Change from Baseline in T2 lesion volume			
Tertiary (FAS)	The absolute volume and change from Baseline to the Month i Visit, where i= 12, 24, in T2 lesion volume by Visit	Descriptive summary statistics.	

14.3.10 Magnetization Transfer Ratio (MTR)

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Change from Baseline in MTR percentage			
Tertiary (FAS)	Change from Baseline in MTR - White Matter (%) at Month 24 Visit.	Mixed-effects linear model for the change from Baseline with the following adjusting factors: • Baseline score, • Age (in years), • EDSS at Baseline (≤3, > 3), • Time between scans (years), • Within-subject correlation. Estimated Least Square Means (LS Means) and corresponding Standard Errors (SE) will be presented by Visit including 2-sided p-values and 95% CI	Missing observations at Baseline: Subjects with a missing Baseline MTR will not be included in the linear model. Missing post-Baseline observations: Missing post-Baseline assessments will not be imputed. The repeated measurement model handles missing post-Baseline assessments under the assumption of MAR.
	Change from Baseline in MTR - Grey Matter (%) at Month 24 Visit.		
	Change from Baseline in MTR - T1 lesions (%) at Month 24 Visit.		
	Change from Baseline in MTR - T2 lesions (%) at Month 24 Visit.		
	Change from Baseline in MTR - T2 perilesions (%) at Month 24 Visit.		
	Change from Baseline in MTR - Putamen (%) at Month 24 Visit.		
	Change from Baseline in MTR - Thalamus (%) at Month 24 Visit.		
	Change from Baseline in MTR - Optic Nerve (%) at Month 24 Visit.		
Tertiary endpoint: Change from Month 6 Visit in MTR percentage			
Tertiary (FAS)	Change from Month 6 Visit in MTR - White Matter (%) at Month 24 Visit.	Descriptive summary statistics.	
	Change from Month 6 Visit in MTR - Grey Matter (%) at Month 24 Visit.		
	Change from Month 6 Visit in MTR - T1 lesions (%) at Month 24 Visit.		
	Change from Month 6 Visit in MTR - T2 lesions (%) at Month 24 Visit.		
	Change from Month 6 Visit in MTR - T2 perilesions (%) at Month 24 Visit.		
	Change from Month 6 Visit in MTR - Putamen (%) at Month 24 Visit.		
	Change from Month 6 Visit in MTR - Thalamus (%) at Month 24 Visit.		
	Change from Month 6 Visit in MTR - Optic Nerve (%) at Month 24 Visit.		

Mixed-effects linear model for repeated measures

As defined in Section 14.3.1 applying adaptations to the endpoints, factors and covariates listed in the table above.

14.3.11 Brain Volume

Brain volume will be provided for Baseline, Month 6 Visit, and Month 24 Visit by central reading for the following volume types:

- Brain Volume (BV), i.e. the total brain volume
- White Matter BV (WMBV)
- Grey Matter BV (GMBV)
- Deep Grey Matter BV (DGMBV)

Percentage brain volume change (PBVC) will be provided for BV from joint image comparison of the central reading for the following changes:

- Baseline to Month 1, 2, 3, 6, 12, 24 Visits
- Month 6 Visit to Month 24 Visit

Percentage white matter / grey matter / deep grey matter volume change from Baseline to Month 24 will be calculated as follows:

- PWMVC = 100 * (WMBV at Month 24 Visit - WMBV at Baseline) / (WMBV at Baseline).
- PWGVC = 100 * (GMBV at Month 24 Visit - GMBV at Baseline) / (GMBV at Baseline).
- PWDGVC = 100 * (DGMBV at Month 24 Visit - DGMBV at Baseline) / (DGMBV at Baseline).

The annualized percentage brain volume change will be calculated by dividing percentage brain volume change by the actual length of follow up between the 2 MRI scans:

- Annualized PBVC = (PBVC * 365.25) / (Duration between the 2 MRI scans in days)
- Annualized PWMBVC = (PWMBVC * 365.25) / (Duration between the 2 MRI scans in days)
- Annualized PGMBVC = (PGMBVC * 365.25) / (Duration between the 2 MRI scans in days)
- Annualized PDGMBVC = (PDGMBVC * 365.25) / (Duration between the 2 MRI scans in days)

Brain Atrophy is the defined by a Brain Volume Loss (BVL) of at least 0.4% during the Treatment Period, i.e.

Yes: annualized PBVC for Baseline to Month 24 $\leq$ -0.4%

No: annualized PBVC for Baseline to Month 24 > -0.4%

If PBVC for Baseline to Month 24 Visit is missing it will be replaced by PBVC for Baseline to Month 12 Visit and if still missing by Baseline to Month 6 Visit, provided the last available assessment is at least 166 days (6 months * 30 days -14 days for Visit Window) after Baseline.

The same cut-off will also be applied for PWMBVC, PGMBVC, and PDGMBVC at Month 24 Visit.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoints: Annualized percentage brain volume change from Baseline			
Tertiary (FAS)	Annualized PBVC at Month i Visit, where i=1, 2, 3, 6, 12 and 24.	Mixed-effects linear model for repeated measures for the change from Baseline with the following adjusting factors: • Baseline value, • Age (in years), • EDSS at Baseline (≤3, > 3), • Visit, • Time between scans (years), • Within-subject correlation. Estimated Least Square Means (LS Means) and corresponding Standard Errors (SE) will be presented by Visit including 2-sided p-values and 95% CI.	Missing observations at Baseline: Subjects with a missing Baseline brain volume will not be included in the linear model. Missing post-Baseline observations: Missing post-Baseline assessments will not be imputed. The repeated measurement model handles missing post-Baseline assessments under the assumption of MAR.
	Annualized PBVC • ≤ -0.4% • > -0.4% during the Treatment Period.	Descriptive summary statistics.	
Tertiary endpoints: Annualized percentage white matter brain volume change from Baseline			
Tertiary (FAS)	Annualized PWMBVC at Month 24 Visit.	Descriptive summary statistics.	
	Annualized PWBVC • ≤ -0.4% • > -0.4% at Month 24 Visit.		

Tertiary endpoints: Annualized percentage grey matter brain volume change from Baseline			
Tertiary (FAS)	Annualized PGMBVC at Month 24 Visit. Annualized PGMBVC • ≤ -0.4% • > -0.4% at Month 24 Visit.	Descriptive summary statistics.	
Tertiary endpoints: Annualized percentage deep grey matter brain volume change from Baseline			
Tertiary (FAS)	Annualized PDGMBVC change at Month 24 Visit. Annualized PDGMBVC • ≤ -0.4% • > -0.4% at Month 24 Visit.	Descriptive summary statistics.	
Tertiary endpoints: Percentage brain volume change from Baseline			
Tertiary (FAS)	PBVC change at Month 24 Visit.	Descriptive summary statistics.	
Tertiary endpoints: Percentage white matter brain volume change from Baseline			
Tertiary (FAS)	PWMBVC change at Month 24 Visit.	Descriptive summary statistics.	
Tertiary endpoints: Percentage grey matter brain volume change from Baseline			
Tertiary (FAS)	PGMBVC change at Month 24 Visit.	Descriptive summary statistics.	
Tertiary endpoints: Percentage deep grey matter brain volume change from Baseline			
Tertiary (FAS)	PDGMBVC change at Month 24 Visit.	Descriptive summary statistics.	
Tertiary endpoints: Percentage Brain Volume change from Month 6 Visit			
Tertiary (FAS)	PBVC at Month 24 compared to Month 6	Descriptive summary statistics.	
Tertiary endpoints: Brain volume			
Tertiary (FAS)	BV at Baseline, Month 6 and 24 Visits.	Descriptive summary statistics.	
Tertiary endpoints: White matter brain volume			
Tertiary (FAS)	WMBV at Baseline, Month 6 and 24 Visits.	Descriptive summary statistics.	
Tertiary endpoints: Grey matter brain volume			
Tertiary (FAS)	GMBV at Baseline, Month 6 and 24 Visits.	Descriptive summary statistics.	

Tertiary endpoints: Deep grey matter brain volume			
Tertiary (FAS)	DGMBV at Baseline, Month 6 and 24 Visits.	Descriptive summary statistics.	

14.3.12 No Evidence of Disease activity

No Evidence of Disease activity (NEDA), also referred to as freedom from disease activity, is a new goal that is emerging in MS treatment. NEDA is a composite measure of disease activity, including relapses, cognition and disability progression, and MRI activity. Since MRI activity is a broad concept, which can correspond to the MRI lesion load or changes in brain volume monitoring brain atrophy, the distinction between NEDA-3 and NEDA-4 will be provided.

NEDA-3

NEDA-3 at Month 24 is defined by the absence of:

- Qualifying Relapses,
- 6-months Confirmed Disability Progression (6MCDP),
- MRI activity,

during the whole Treatment Period. If the information for one of the components is unknown, and none of the other components are observed, NEDA-3 will be classified as "unknown". Thus, NEDA-3 can be derived from its components as follows:

- Yes: all components = "No",
- No: at least one of the components =" Yes",
- Unknown: Otherwise.

NEDA-3 (frequent MRI)

NEDA-3 at Month 24 is defined by the absence of:

- Qualifying Relapses,
- 6-months Confirmed Disability Progression (6MCDP),
- MRI activity (frequent MRI),

during the whole Treatment Period. If the information for one of the components is unknown, and none of the other components are observed, NEDA-3 will be classified as "unknown". Thus, NEDA-3 can be derived from its components as follows:

- Yes: all components = "No",
- No: at least one of the components =" Yes",
- Unknown: Otherwise.

NEDA-4

NEDA-4 at 24 Month is defined as the composite endpoint of NEDA-3 and the absence of brain atrophy.

NEDA-4 (frequent MRI)

NEDA-4 (frequent MRI) at Month 24 is defined by the composite endpoint of NEDA-3 (frequent MRI) and the absence of brain atrophy.

Qualifying Relapse

- Yes: qualifying relapses reported during the Treatment Period,
- No: study completed, and no qualifying relapse reported during Treatment Period,
- Unknown: otherwise.

6-Months Confirmed Disability Progression (6MCDP)

A Sustained Increase in EDSS score, is defined by an increase of:

- at least 1.5 points if the Baseline EDSS score was 0, or
- at least 1 point if Baseline EDSS score was between 0.5 and 4.5 inclusively, or
- at least 0.5 point if the Baseline EDSS score was at least 5,

that occurs over a 6-month time Period.

The increase will be defined as sustained when it occurs on two post-Baseline Visits, which are at least 166 days (6 months × 30 - 14 days Visit Window) apart and no observations at any other Visit (including unscheduled Visits) in between are less than the defined increase.

The occurrence of a 6MCDP is defined as:

- Yes: sustained increase in EDSS score that started during the Treatment Period,
- No: at least 2 post-Baseline EDSS assessments that are 166 (or more) days apart are available and no sustained EDSS progression that started during the Treatment Period,
- Unknown: Otherwise.

Start date of the 6MCDP is the start date of the first sustained increase in EDSS.

MRI activity:

- Yes: At least one T1 Gd+ at any scan assigned to Month 6, Month 12, Month 18, Month 24 Visit, or at least one active T2 during any of the following Periods: Baseline to Month 6, Month 6 - Month 12, Month 12 - Month 18, Month 18 – Month 24 Visits.

- No: T1 Gd+ = 0 at all scans assigned to Month 6, Month 12, Month 18, Month 24 Visit that have a value and at least one T1 Gd+ value from Month 18 or Month 24 Visit available, and all active T2 = 0 during any of the following Periods: Baseline - Month 6, Month 6 - Month 12, Month 12 - Month 18, Month 18 - Month 24 Visits that have a value and at least one active T2 value from periods Month 12 - Month 18 or Month 18 - Month 24 Visits available.

- Unknown: Otherwise.

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Brain Atrophy

- Yes: Annualized percentage brain volume change during the Treatment Period < -0.4% (see Section 14.3.11),
- No: Annualized percentage brain volume change during the Treatment Period ≥ -0.4%,
- Unknown: Otherwise.

Analysis of NEDA

NEDA and its components will be analyzed with a logistic regression with adjusting factors age (in years) and EDSS at Baseline (≤3, >3).

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: NEDA at 24 months			
Tertiary (FAS)	NEDA-3 during Treatment Period	Logistic regression: Adjusting factors: • Age (in years), • EDSS at Baseline (≤3, >3). Estimated probability and corresponding Standard Errors (SE) will be presented including 2-sided p-values and 95% CIs.	Unknown status: Subjects with an unknown status will be excluded from the logistic regression. Missing covariate or stratification information will be imputed as specified in Section 9.
Tertiary (FAS)	NEDA-3 (frequent MRI) during Treatment Period		
Tertiary (FAS)	NEDA-4 during Treatment Period		
Tertiary (FAS)	NEDA-4 (frequent MRI) during Treatment Period		
Tertiary (FAS)	Any 6MCDP during Treatment Period		
Tertiary (FAS)	Any MRI activity during the Treatment Period		
Tertiary (FAS)	Any MRI activity (frequent MRI) during the Treatment Period		
Tertiary (FAS	Brain Atrophy during Treatment Period		
Tertiary (FAS)	Any Qualifying Relapse during the Treatment Period		

All components of NEDA will be listed by subject.

14.3.13 No Evidence of Progression or Active Disease

No Evidence of Progression or Active Disease (NEPAD) is a composite measure, evolution of NEDA-3, including relapses and different measurements of disability progression and MRI activity.

NEPAD at Month 24 is defined as the composite endpoint of NEDA-3 and the absence of:

- 20% progression on T25-FW,
- 20% progression on 9HPT,

during the Treatment Period.

20% confirmed T25FW progression

20% confirmed progression on T25FW is defined by an increase of at least 20% from T25FW Baseline that is sustained over a 6-month time Period.

The increase will be defined as sustained when it occurs on two post-Baseline Visits, which are at least 166 days (6 months * 30 -14 days Visit Window) apart and no score at any other Visit including unscheduled Visits in between is less than the defined increase.

The occurrence of a 20% confirmed T25FW progression is defined as:

- Yes: sustained T25FW progression that started during the Treatment Period.
- No: at least 2 post-Baseline T25FW assessments that are 166 (or more) days apart are available and no sustained T25FW progression that started during the Treatment Period.
- Unknown: Otherwise.

Only T25FW assessments with the same assistance devices as at Baseline will be analyzed. T25FW trials which couldn't be finished by the subjects will be imputed with 3 minutes (see Section 14.3.17).

20% confirmed 9HPT progression

20% confirmed progression on 9HPT is defined by an increase of at least 20% from 9HPT Baseline that is sustained over a 6-month time Period.

The increase will be defined as sustained when it occurs on two post-Baseline Visits, which are at least 166 days (6 months * 30 - 14 days Visit Window) apart and no score at any other Visit including unscheduled Visits in between is less than the defined increase.

The occurrence of a 20% confirmed 9HPT progression is defined as:

- Yes: sustained 9HPT progression that started during the Treatment Period.
- No: at least 2 post-Baseline 9HPT assessments that are 166 (or more) days apart and no sustained 9HPT progression that started during the Treatment Period.
- Unknown: Otherwise.

Analysis of NEPAD

NEPAD will be analyzed with a logistic regression with adjusting factors age (in years) and EDSS at Baseline (≤3, >3).

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: NEPAD at 24 months			
Tertiary (FAS)	NEPAD during the Treatment Period	Same as in the Tertiary Analysis of NEDA (Section 14.3.12)	Same as in the Tertiary Analysis of NEDA (Section 14.3.12)
Tertiary (FAS)	Confirmed T25FW progression during the Treatment Period		
Tertiary (FAS)	Confirmed 9HPT progression during the Treatment Period		

14.3.14 Changes in SDMT outcome at the end of 6, 12, 18 and 24 months compared to Baseline

The SDMT (Symbol Digit Modalities Test) presents a series of nine symbols, each paired with a single digit in a key at the top of a standard sheet of paper. An adapted version of the test is presented in the protocol. Subjects are asked to voice the digit associated with each symbol as rapidly as possible for 90 sec. The SDMT score is the number of correct digits over the 90 sec time span.

Minimal decline in cognitive function is defined by:

- Yes: Change from Baseline in SDMT ≥ -4 at the Month 24 Visit
- No: Change from Baseline in SDMT < -4 at the Month 24 Visit
- Missing: Baseline or Month 24 Visit value is not available

The observed results and changes from Baseline in the SDMT and scaled scores of the SDMT will be tabulated by Visit for the FAS (see Section 18.2).

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Changes in SDMT outcome at the end of 6, 12, 18 and 24 months compared to Baseline			
Tertiary (FAS)	Change from Baseline in SDMT (raw and scaled scores) at Month i Visit, where i= 6, 12, 18 and 24.	Descriptive summary statistics.	
	Minimal Decline in Cognitive Function at Month 24 Visit compared to Baseline	Descriptive summary statistics	Missing values will be included in the denominator and presented as a separate category.

14.3.15 Changes in level of disability as measured by EDSS

The Expanded Disability Status Scale (EDSS) ranges from 0 to 10 in increments of 0.5 on an ordinal scale. Higher scores represent a higher level of disability. Details of the EDSS scoring are included in the appendix of the study protocol.

The observed EDSS and the change from Baseline will be presented by Visits using summary statistics (median, quartiles, min, max) and by the following categorization for each Visit:

- ≤3,
- >3-<6,
- ≥6.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary endpoint: Changes in level of disability as measured by EDSS at Month 6, 12, 18, and 24 compared to Baseline			
Tertiary (FAS)	Changes from Baseline of EDSS at Month i Visit, where i= 6, 12, 18 and 24.	Descriptive summary statistics for the median and quartiles.	

Tertiary (FAS)	EDSS categories (<3, 3-<6, ≥6) at Baseline, Month 6, 12, 18 and 24 Visits.	Descriptive summary statistics.	Missing values will be included in the denominator and presented as a separate category.

14.3.16 Changes in level of disability as measured by 9HPT

The 9HPT should be completed at Baseline and then at Month 6, 12 18, and 24 Visit to measure the level of disability over time. The subjects have to stick 9 pegs in 9 holes and place them back. That will be done twice for each hand. The mean of the 4 stop times will be analyzed. At least one stop time must be recorded, otherwise, the Visit will be considered as missing. Details of the 9HPT are included in the appendix of the study protocol.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Changes in level of disability as measured by 9HPT at Month 6, 12, 18, and 24 Visit compared to Baseline			
Tertiary (FAS)	Change from Baseline in mean time of the 9HPT to the Month i Visit, where i= 6, 12, 18, and 24.	Mixed-effects linear model for repeated measures, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)

14.3.17 Changes in level of disability as measured by T25FW

T25FW is a quantitative mobility and leg function performance test based on a timed walk over 25 feet (approximately 7.6 meters). Administration time will vary depending upon the ability of the subject. Subjects have to twice walk a trial of 25 feet. The time limit for each trial is 3 minutes. At least one trial has to be completed to calculate the mean time for a Visit. If the subjects couldn't finish a trial, the trial will be scored with 3 minutes. T25FW performed with a different assistance device as compared to what was used at Baseline will be considered as "changed device" and will not be included in the statistical analysis. Details of the T25FW are included in the appendix of the study protocol.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Changes in level of disability as measured by T25FW at Month 6, 12, 18, and 24 Visit compared to Baseline			
Tertiary (FAS)	Change from Baseline in mean time of the T25FW to the Month i Visit, where i= 6, 12, 18, and 24.	Mixed-effects linear model for repeated measures, same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)	Same as in Tertiary Analysis for Change from Baseline in CUA lesion count (see Section 14.3.1)

14.3.18 Annualized Relapse Rate (ARR) between Baseline and 12/24 months

The unadjusted ARR will be calculated for the Treatment Period, Course 1 Treatment Period and Course 2 Treatment Period.

The unadjusted ARR for a subject *i* is defined as the number of relapses per year:

- ARR for subject *i* = number of relapses during the Period / person-years of subject *i*,
- Person-years for subject *i* = Period (in days) / 365.25.

The unadjusted population ARR is the mean of all subject's ARRs. The unadjusted ARR will be calculated for all relapses, as well as the qualifying relapses (ARR_{qual}), as reported in the eCRF.

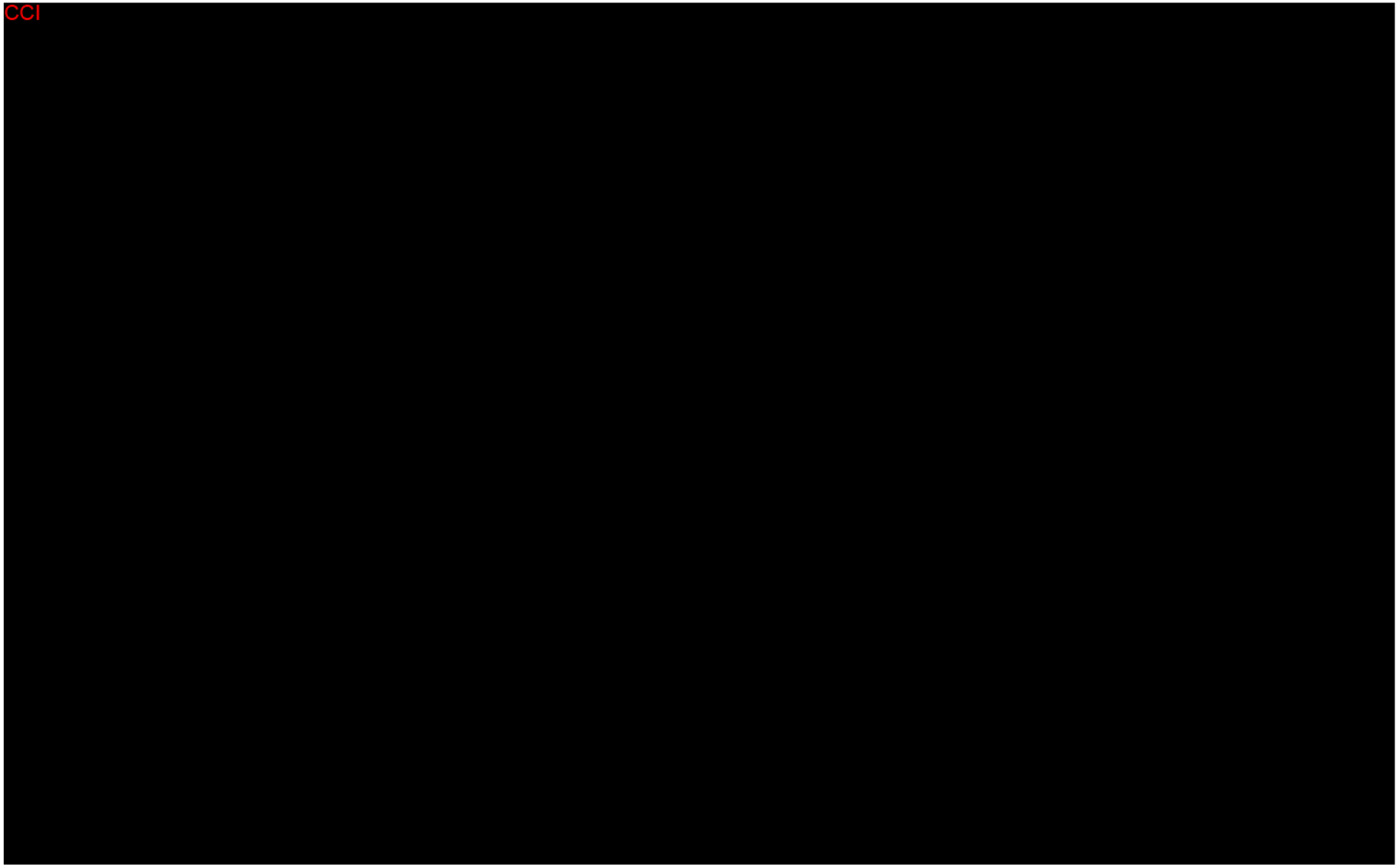
Relapses will be counted for the defined time Period, if the date of onset of the relapse is within the defined time Period. Incomplete or missing onset dates will be imputed as specified in Section 9.

The number of subjects with (qualifying) relapses, the number of (qualifying) relapses, person-years and the unadjusted population ARR will be presented for the Treatment Period, Course 1 Treatment Period and Course 2 Treatment Period. Also, the number of subjects with relapses and number of relapses which were treated with steroids or leading to hospitalization will be presented separately. For the Interim Analysis the different relapse counts up to the month 6 Visit will be presented without the ARR.

In addition, the relapse rate will be analyzed using a Poisson regression model with count of relapses as dependent variable and with fixed effects for age (in years) and EDSS at Baseline (≤3, >3). The log of the duration of the treatment Period (precision in days) will be the offset variable in the model.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Tertiary endpoint: Annualized relapsed rate (ARR) between Baseline and Month 12 and Month 24			
Tertiary (FAS)	ARR during the Treatment Period	Poisson regression for number of relapses. Adjusting factors: • Age (in years), • EDSS at Baseline (≤3/>3). • Log of the duration of the Treatment Period (in days) as offset. Estimated mean ARR and corresponding Standard Errors (SE) will be presented, including 2-sided p-values and 95% CIs. In addition, the unadjusted ARR will be presented descriptively.	The analysis will consider the different observation Periods of early withdrawals by including the treatment Period as offset in the analysis. This strategy is assuming MAR .
Tertiary (FAS)	ARR during the Course 1 Treatment Period		
Tertiary (FAS)	ARR during the Course 2 Treatment Period		
Tertiary (FAS)	ARR_{qual} during the Treatment Period		
Tertiary (FAS)	ARR_{qual} during the Course 1 Treatment Period		
Tertiary (FAS)	ARR_{qual} during the Course 2 Treatment Period		
Tertiary (FAS)	ARR leading to hospitalization during the Treatment Period		
Tertiary (FAS)	ARR requiring steroid treatment during the Treatment Period		

For the 6-month IA, all relapses during first 6 months will be listed together with relevant MRI results (T1, T2 and CUA lesion counts) by subject.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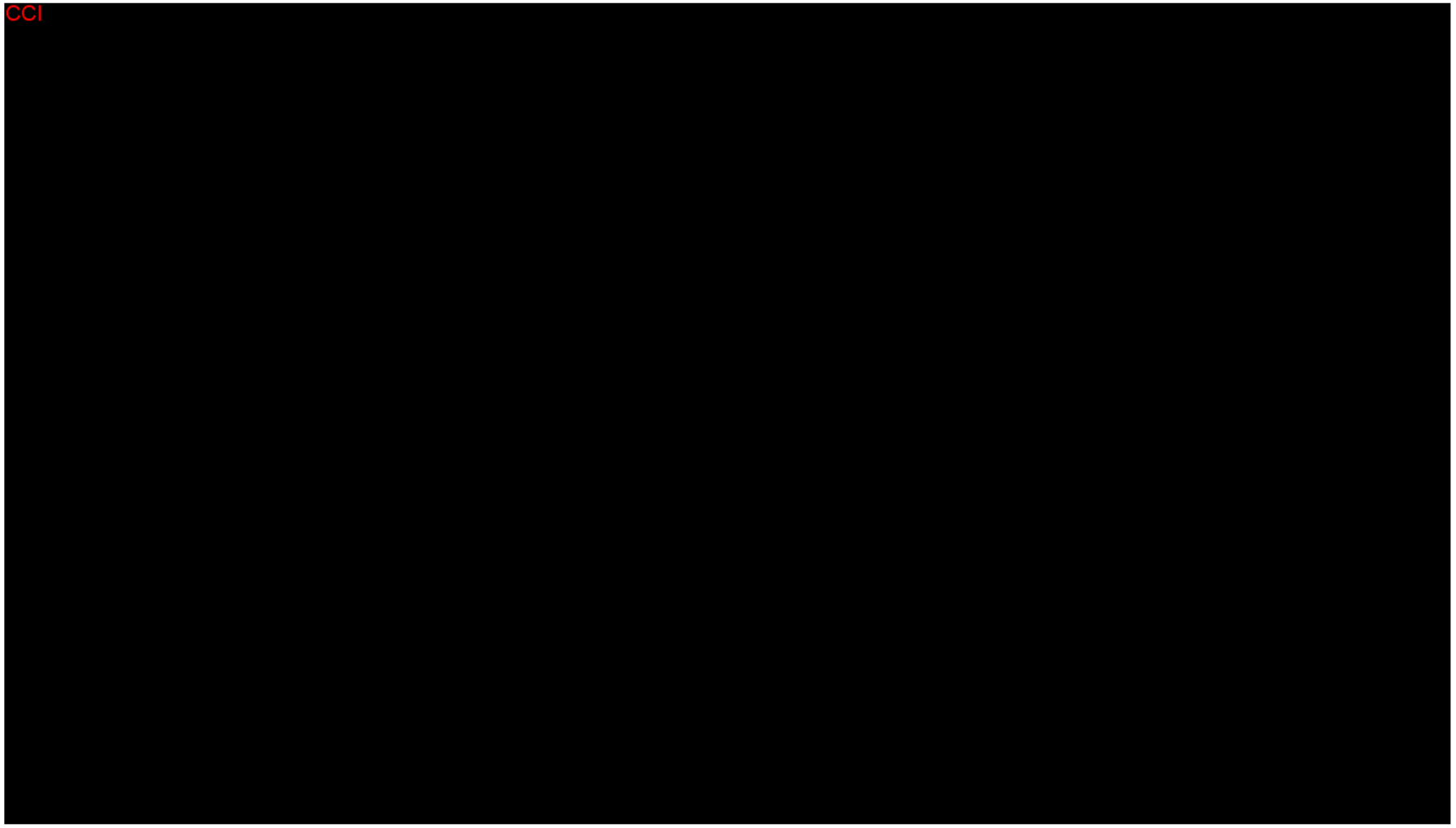
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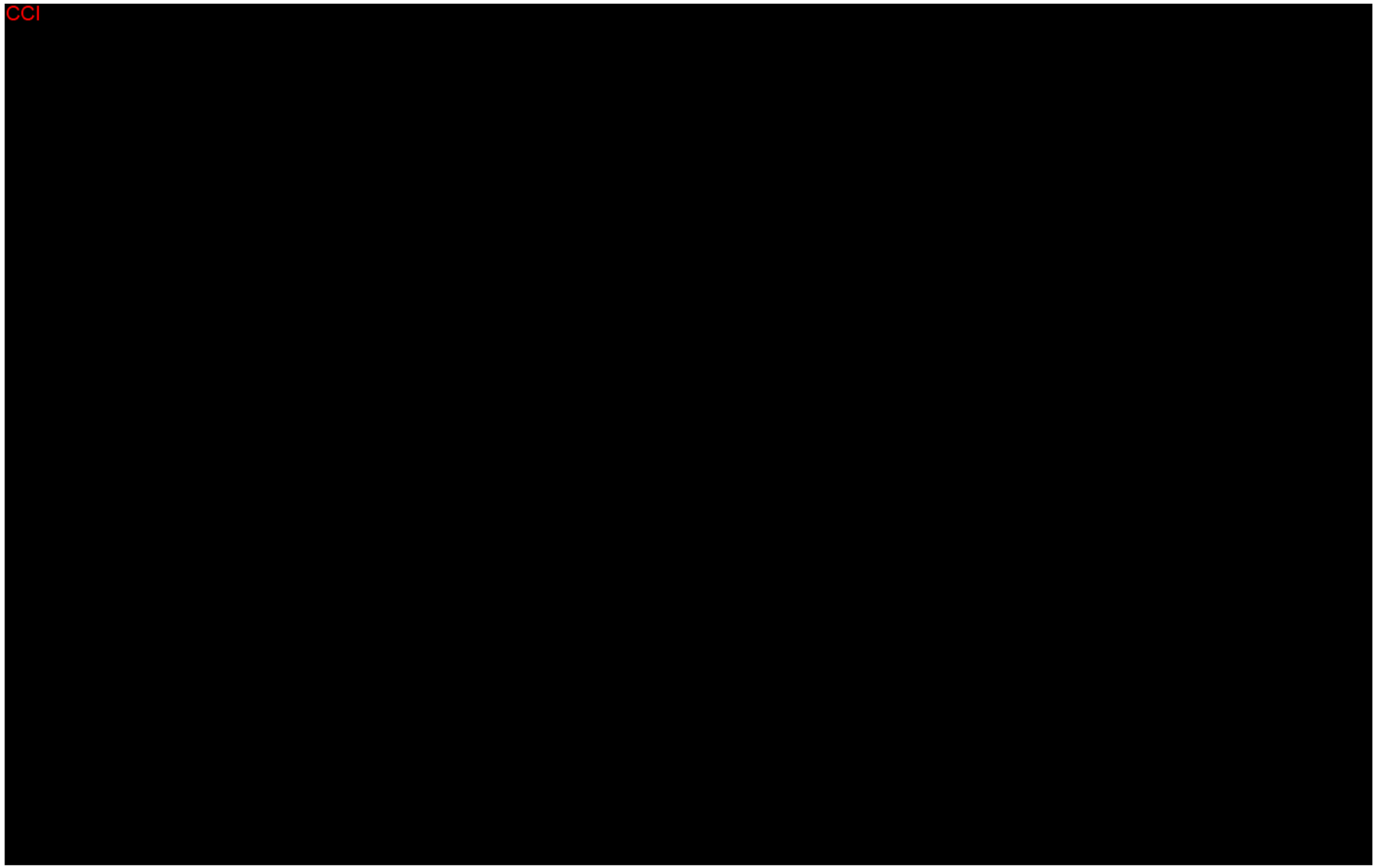
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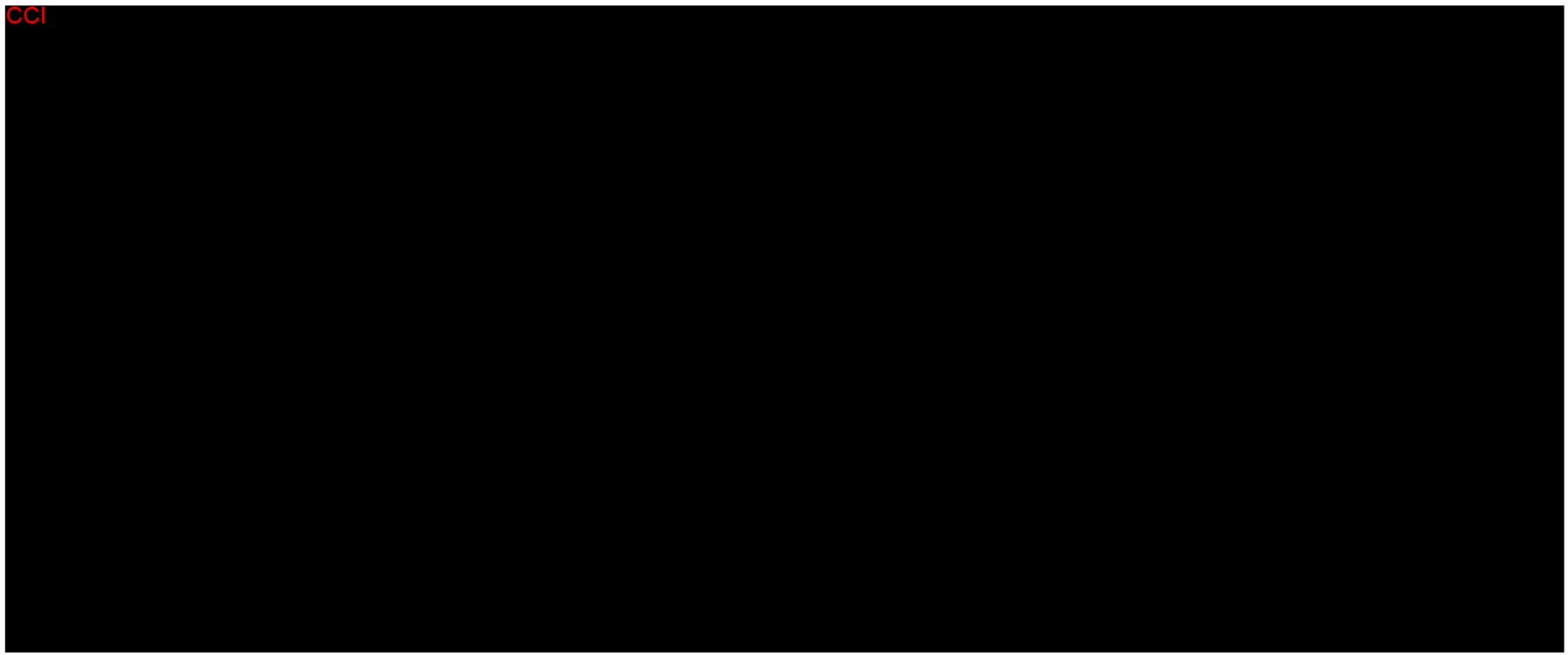


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15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

Safety analyses will be done on the SAF. Unless otherwise specified, the safety analysis will be done for interim and final analysis.

15.1 Adverse Events

Treatment emergent adverse events (TEAEs) are those events with onset dates occurring within the Treatment Period (see Section 9 for definition).

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

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially and the onset month and year or the onset year are equal to the start of study medication, then the onset date will be replaced by the start date of study medication or AE resolution date whichever is earlier.
- In all other cases the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject'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.

15.1.1 All Adverse Events

TEAEs will be summarized using MedDRA PT as event category and MedDRA primary SOC body term as Body System category overall and by HRA subgroups (HRA and non-HRA).

Unless otherwise stated, adverse events will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order.

Adverse events related to study treatment are those events with relationship missing, unknown or related.

The following overall frequencies of subjects with the corresponding TEAEs will be prepared. In addition, the tables will be provided by PT and primary SOC in alphabetical order:

- Any AE,
- Any study treatment related AEs,
- Any serious AEs,
- Any non-serious AEs,
- Any study treatment related serious AEs,
- Any AE by severity (mild, moderate, severe),
- Any study treatment related AE by severity (mild, moderate, severe),
- Any AEs leading to death (AEs with outcome "fatal"),
- Any study treatment related AEs leading to death (AEs with outcome "fatal").

Summary table for non-serious adverse events applying frequency threshold of 5% will be provided by SOC and PT.

Summary tables for serious and non-serious adverse events applying frequency threshold of 5% sorted by decreasing frequency will be provided by PT.

All AE by worst severity (Mild or worse, moderate or worse, severe) will be presented by SOC and PT.

All AEs including non-treatment emergent AEs will be listed by subject for the SAF.

Exposure Adjusted Incidence Rate

Exposure adjusted incidence rates (EAIR) are calculated as number of subjects with AE divided by the sum of the individual times in years of all subjects in the safety population from start of study medication to first onset of AE or end of treatment Period, whichever occurs first.

The exact Poisson 95% confidence intervals for the EAIR are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm [1], 1990):

$$LCI = \frac{\chi^2_{2n,\frac{a}{2}}}{2 \times t},$$

$$UCI = \frac{\chi^2_{2(n+1),1-\frac{a}{2}}}{2 \times t},$$

where t is the sum of the individual times in years of all subjects and n is the number of subjects with a specific AE for the EAIR, which will be the basis for the number of the degrees of freedom for the chi-square quantile for the upper tail probability χ^2.

Exposure adjusted incidence rates of TEAEs will be presented overall and by SOC and PT.

The following table will be provided:

- Exposure adjusted incidence rates of AEs by SOC and PT.

15.1.2 Adverse Events Leading to Treatment Discontinuation

The following overall frequency tables will be prepared for the adverse event actions. Tables will be provided by PT and primary SOC in alphabetical order:

- Any AE leading to temporary discontinuation of study drug,
- Any AE leading to permanent discontinuation of study drug,
- Any AE leading to dose reduction of study treatment.

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

15.2.1 Deaths

Any discontinuations due to death (see Section 10.1) and any AE leading to death will be tabulated (see Section 15.1.1).

A summary table of observed Deaths (from "Study Termination" eCRF page) will be provided together with TEAEs with fatal outcome by PT.

15.2.2 Serious Adverse Events

The statistical analysis and reporting of serious adverse events are defined in Section 15.1.1. In addition, all serious adverse events will be listed.

15.2.3 Other Significant Adverse Event

TEAEs associated to COVID-19

The frequency of TEAEs associated to COVID-19 will be presented. The relevant events will be identified based on the SMQ COVID-19 (narrow scope) and will be presented by SOC and PT.

Fatigue

The prevalence of fatigue will be presented for each month of the Course 1 Treatment Period and separately for each month of the Course 2 Treatment Period. The prevalence at a given month is defined as:

(Number of subjects with fatigue during the month/ Number of subjects with fatigue during the month or still in the study at the end of the month) * 100,
where subjects with fatigue during the month are all subjects who had at least one reported TEAE with PT equal to 'Fatigue' that either started during the month or is still ongoing from the previous month.

If the end date of the AE is partially or completely missing and the AE is not reported as ongoing, the end date will be imputed as follows:

- Day missing but month and year available: last day of the month,
- Day and month missing: last day of the year but not later than end of Treatment Period 2,
- Completely missing: end of Treatment Period 2

The results will be presented in a tabular as well as graphical manner. Course 1 and 2 Treatment Periods as well as duration of a month is defined in Section 9.

15.3 Clinical Laboratory Evaluation

Lymphocyte counts from local laboratory will be used for summary statistics and shift tables. They will be classified according to the NCI-CTCAE. The classification will be derived only from the laboratory results at a given assessment, thus ignoring the underlying syndrome.

The Treatment Course 2 can be delayed because of Lymphocyte count below 800 cells/mm³ at the Month 12 Visit. In this case, the Lymphocyte count can be measured several times between the Month 12 Visit and the start of Treatment Course 2. Lymphocyte counts at or after the Visit start date of the Month 12 Visit and before or at the start date of the Treatment Course 2 will be displayed as followed:

- The earliest Lymphocyte count will be assigned to the Month 12 Visit,
- The latest Lymphocyte will be assigned to the Month 12b Visit,
- All other Lymphocyte count will be assigned to unscheduled Visits.

A Lymphocyte count can be assigned to the Month 12 Visit and Month 12b Visit if just one count is available. If the Treatment Course 2 wasn't started, only the earliest Lymphocyte count will be assigned to the Month 12 Visit.

The worst on-study grade (i.e., on, or after, first study treatment administration) will be summarized by subject considering only subjects with post-Baseline laboratory samples: Laboratory tests by NCI-CTC grade (0, 1, 2, 3, 4, any).

Lymphocyte counts will be examined for trends using descriptive statistics (mean, SD, median, Q1, Q3, minimum, and maximum) of actual values and changes from Baseline to each scheduled Visit including Month 12b Visit over time. If for a particular Visit a different local laboratory than normal laboratory was used (due to COVID-19 pandemic), values collected during that Visit will not be included in the descriptive statistics.

Shift tables of Baseline versus endpoint (as well as the worst value at any post-Baseline Visit) will be presented. Abnormalities classified according to NCI-CTCAE toxicity grading will be described using the worst grade.

All Lymphocyte counts will be listed by subject for the SAF.

Positive results of the tuberculosis and serology tests that do not comply with the protocol will be listed.

15.4 Vital Signs

The maximum changes of vital sign measurements from Baseline to maximum change after start of 1st treatment will be grouped as follows:

Heart rate increase from Baseline <100 bpm; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
Heart rate decrease from Baseline <100 bpm; ≥ 100 bpm	≤20 bpm, >20 – 40 bpm, >40 bpm
SBP increase from Baseline <140 mmHg; ≥ 140 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
SBP decrease from Baseline <140 mmHg; ≥ 140 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP increase from Baseline <90 mmHg; ≥ 90 mmHg	≤20 mmHg, >20 – 40 mmHg, >40 mmHg
DBP decrease from Baseline <90 mmHg; ≥ 90 mmHg,	≤20 mmHg, >20 – 40 mmHg, >40 mmHg

For each subject, the worst change during the treatment Period will be considered. Missing values will be presented as a separate category.

The following will be prepared for vital sign parameters as grouped above considering only subjects with post-Baseline values:

- Summary of Maximal Shifts (changes in categories),
- Listing of highest change per subject.

15.5 Other Safety or Tolerability Evaluations

The results of the physical examination will not be presented in any statistical analysis or listing. Abnormalities occurring, or worsening, during the study will be reported as AE.

Safety Findings during Central Review are reported back to the sites for further clinical assessment and reporting as AE, as outlined in the Review Charter. Thus, no separate statistical reporting of the Safety MRI central review data will be done.

Positive pregnancy tests or pregnancy tests not done without a reason, will be listed for the SAF.

16 Analyses of Other Endpoints

Not applicable.

17 References

[1] Ulm, K. "A simple method to calculate the confidence interval of a standardized mortality ratio (SMR)." American journal of epidemiology vol. 131,2 (1990): 373-5. doi:10.1093/oxfordjournals.aje.a115507

[2] Brunner, E., Domhof, S. und Langer, F. (2002) Nonparametric Analysis of Longitudinal Data in Factorial Experiments. Wiley, New York.

[3] Independent Review Charter for Counting Brain MRI Lesions - MS700568_0022, Version 2.0, 07 November 2019

[4] Parmenter, Brett A et al. "The utility of regression-based norms in interpreting the minimal assessment of cognitive function in multiple sclerosis (MACFIMS)." Journal of the International Neuropsychological Society: JINS vol. 16,1 (2010): 6-16. doi:10.1017/S1355617709990750

[5] Rubin, D. B. (1987). Multiple Imputation for Nonresponse in Surveys. New York: John Wiley & Sons.

[6] Independent Review Charter for Lesion Counting for the Tertiary Endpoint - MS700568_0022, Version 2.0, 24 February 2021

[7] Independent Review Charter for Advanced MRI - MS700568_0022, Version 1.0, 17 February 2021

[8] Data Transfer Specification - MS700568_0022 - MRI-based endpoint values, Version 3.1, 08 July 2021 (specification provided by SIENA imaging)

[9] Data Transfer Agreement - MS700568_0022 - Biomarker test results, Version 10.0, 06 August 2021 (specification provided by Parexel International)

[10] Appendix Parameter Mapping to Data Transfer Agreement - MS700568_0022 – Biomarker test results, Version 5.0, 06 August 2021 (specification provided by Parexel International)

18 Appendices

18.1 Appendix 1: List of DMDs

DMDs	Preferred Term
Alemtuzumab* (Campath, MabCampath, Lemtrada)	ALEMTUZUMAB
Daclizumab* (Zinbryta)	DACLIZUMAB
Dimethyl fumarate (Tecfidera)	DIMETHYL FUMARATE
Fingolimod* (Gilenya)	FINGOLIMOD FINGOLIMOD HYDROCHLORIDE
Glatiramer Acetate (Copaxone)	GLATIRAMER GLATIRAMER ACETATE
Immunoglobulins	IMMUNOGLOBULIN HUMAN NORMAL IMMUNOGLOBULINS IMMUNOGLOBULINS NOS
Interferon beta (Avonex, Rebif, Betaferon, Extavia, Plegridy)	INTERFERON INTERFERON BETA INTERFERON BETA-1A INTERFERON BETA-1B PEGINTERFERON PEGINTERFERON BETA-1A
Mitoxantrone (Novantrone)	MITOXANTRONE MITOXANTRONE HYDROCHLORIDE
Natalizumab* (Tysabri)	NATALIZUMAB
Non-approved investigational DMDs* (monoclonal antibodies, antiS1PR, laquinimod etc)	DIROXIMEL FUMARATE INVESTIGATIONAL DRUG LAQUINIMOD OFATUMUMAB OPICINUMAB OTHER ANTINEOPLASTIC AGENTS OZANIMOD
Ocrelizumab* (Ocrevus)	OCRELIZUMAB
Off-label immunosuppressants (azathioprine, mycophenolate, cyclophosphamide)	AZATHIOPRINE CYCLOPHOSPHAMIDE METHOTREXATE
Siponimod*	SIPONIMOD
Teriflunomide (Aubagio)	TERIFLUNOMIDE
DMDs marked with a * are second line DMDs, which are not allowed as a previous medication according to the study protocol.	

Subjects who have taking any of the listed DMDs according to the "Relevant Previous Medication" eCRF page will be categorized as DMD pre-treated. All other subjects will be considered as pre-treatment naïve. The list may be extended during medical review in case that new or other DMDs will be applied during the study.

18.2 Appendix 2: SDMT Scaled Score

Scaled score	SDMT
2	
3	<43
4	43-45
5	46
6	47-50
7	51-54
8	55-56
9	57-59
10	60-63
11	64-66
12	67-69
13	70-72
14	73-74
15	75-78
16	79
17	80-87
18	>87

Parmenter et al. [4], JINS 2010;16:6-16

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Signature Page for VV-CLIN-280097 v4.0

Approval	PPD

Signature Page for VV-CLIN-280097 v4.0