Integrated Analysis Plan

Clinical Trial Protocol Identification No.	MS700568_0021
Title	A 2-year Prospective Study to Assess Health-related Quality of Life in Subjects with Highly-active Relapsing Multiple Sclerosis Treated with Mavenclad®
Trial Phase	IV
Investigational Medicinal Product(s)	Mavenclad®
Clinical Trial Protocol Version	14 December 2018 / Version 2.0
Integrated Analysis Plan Author	**Coordinating Author** Biostatistics, PPD PPD

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Integrated Analysis Plan Reviewers	

Function	Name
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PPD	

Signature Page

Integrated Analysis Plan: MS700568_0021

A 2-year Prospective Study to Assess Health-related Quality of Life in Subjects with Highly-Active Relapsing Multiple Sclerosis Treated with Mavenclad®

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

Merck responsible	Date	Signature
PPD Lead Biostatistician	Via Veeva Vault approval process	

1 Table of Contents

2 List of Abbreviations and Definition of Terms

CCI	
ADaM	Analysis Data Model
AE	Adverse Event
ARR	Annualized Relapse Rate
ATC	Anatomical Therapeutic Chemical classification
CCI	
BVMT-R	Brief Visuospatial Memory Test – Revised
CDISC	Clinical Data Interchange Standards Consortium
CDP	Confirmed Disability Progression
CI	Confidence Interval
COVID-19	Coronavirus disease 2019
CRF	Case Report Form
CSR	Clinical Study Report
CVLT-II	California Verbal Learning Test – Second edition
DMD	Disease Modifying Drug
EAIR	Exposure adjusted incidence rates
CCI	
ET	Early Termination
FAS	Full Analysis Set
CCI	
CCI	
HRQOL	Health Related Quality of Life
ICH	International Conference on Harmonization
IA	Interim Analysis
IAP	Integrated Analysis Plan
iRT	Interactive Response Technology
ITT	Intention to Treat
CCI	
LS	Least Square
MCID	Minimally Clinically Important Difference

MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NA	Not Applicable
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSQoL-54	Multiple Sclerosis Quality of Life-54 Questionnaire
CCI	
eCRF	electronic Case Report Form
ePRO	electronic Patient Reported Outcomes
PBVC	Percentage brain volume change
PD	Protocol Deviation
PDGMVC	Percentage deep grey matter volume change
PGMVC	Percentage grey matter volume change
PML	Progressive Multifocal Leukoencephalopathy
PT	Preferred Term
PWMVC	Percentage white matter volume change
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SDTM	Study Data Tabulation Model
SF-36	36-Item Short Form Health Survey
SOC	System Organ Class
CCI	
TCS-1	Treatment Completer Set – Year 1
TCS-2	Treatment Completer Set – Year 2
TEAE	Treatment Emergent Adverse Event
TLF	Tables, Listings, and Figures
TSQM v1.4	Treatment Satisfaction Questionnaire Medication version 1.4

WHO-DD	World Health Organization Drug Dictionary

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4 Purpose of the Integrated Analysis Plan

The purpose of this Integrated Analysis Plan (IAP) is to document technical and detailed specifications for the interim and final analyses of data collected for protocol MS700568_0021. 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. The IAP specifies also a 1-year interim analysis, which is not planned in the protocol, and any additional analysis to describe the potential impact of the COVID-19 pandemic. Also, an additional Baseline analysis was performed, which is not mentioned in the protocol, and will be described and reported separately.

5 Objectives and Endpoints

	Objective	Endpoint	IAP section
Primary Objective	To assess the health-related quality of life (HRQoL) through the MSQoL-54 scale in highly-active relapsing multiple sclerosis (RMS) subjects treated with Mavenclad® for 2 years (24 months).	Primary Endpoint • Changes in MSQoL-54 at 24 months compared to Baseline, i.e. the changes in the physical and mental health composite scores.	14.1
Secondary Objective	To assess treatment satisfaction through the Treatment Satisfaction Questionnaire Medication (TSQM) v1.4 questionnaire in highly active RMS subjects at 6 months of treatment with Mavenclad®.	Secondary Endpoint • Treatment global satisfaction assessed by TSQM v1.4 at 6 months.	0
CCI			

6 Overview of Planned Analyses

The following analyses are planned for the study:

- Interim analysis (IA) after all subjects have completed the 6-month assessment,
- IA after all subjects have completed the 1-year (Month 12a Visit) assessments,
- Final analysis at the end of the study.

The 1-year IA is not specified in the protocol. The approval to perform the unplanned IA was given 30 July 2020.

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

6.1 Interim Analysis

6.1.1 6-month Interim Analysis

An interim analysis will be undertaken after all subjects have completed the 6-month assessment. As the primary endpoint is not available at this time, the interim analysis will focus on the secondary endpoint which is the treatment global satisfaction assessed by TSQM v1.4 at Month 6 Visit which will be analyzed with a mixed linear regression model overall and by the subgroup, "Previous treatment with Disease Modifying Drugs (DMDs)", see Section 0 for details.

The interim analysis will be considered as supportive of the 24-month analysis (final analysis). Due to the exploratory nature of the study, no alpha spending was planned to control for overall type-I-error inflation.

In addition, the Interim Analysis will describe the following characteristics of the study population:

- Disposition (Section 10.1) including and up to the cut-off point,
- Baseline Characteristics including MS Disease Characteristics (Section 11),
- Relevant Previous Medications (Section 12),

and will include the following endpoints:

- Treatment Effectiveness, Side effects, and Convenience assessed by TSQM v1.4 at the Month 6 Visit (Section 0),
- Changes in level of disability as measured by CCI [redacted] at the Month 6 Visit compared to Baseline (Section 14.3),
- Relapse reports including and up to the cut-off point (Number and Percentage of Subjects with (qualifying) relapses),
- Occurrences of TEAEs and SAEs as well as Lymphocyte counts including and up to the cut-off point (Section 15).

The characteristics will be summarized descriptively up to Month 6 Visit in the same way as for the final analysis.

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 2	Month 6
Informed Consent	X			
Demographic	X			
iRT		X		
Disease History	X			
CCI				
Lymphocyte Count	X	X	X	X
Treatment Satisfaction (TSQM v1.4)				X
Treatment Administration		X		
Relapse Report			X	X
AEs		X	X	X
Treatment and Study Termination		X	X	X
Relevant Previous Medication	X			

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

All events 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).

All data included in the IA will undergo a data cleaning process, however, as the key data point is an ePRO and no decisions on further study conduct are based on this IA, it is not required to have all data 100% cleaned. The quality of the data will be reviewed during the Data Review Meeting.

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.

6.1.2 1-year Interim Analysis

A second unplanned IA will be undertaken after all subjects have completed the initial 12-month assessment.

The interim analysis will focus on the new defined tertiary endpoint, the change in Multiple Sclerosis Quality of Life-54 (MSQoL 54) physical and mental health composite scores at the Month 12 Visit compared to Baseline, which will be analyzed applying the same methodology as specified for the primary endpoint the MSQoL 54 at Month 24 (see section 14.1 for details) except for the repeated visit effect as there is only one post-baseline assessment in this analysis. As a sensitivity analysis, the analysis will be repeated by the subgroup "Previous treatment with DMDs" (Section 8.2). In order to evaluate a potential impact of the Coronavirus disease 2019 (COVID-19) pandemic on the QoL of patients, the analysis will also be repeated by a subgroup of patients that had their Month 12 MSQoL assessment after the start of the COVID-19 pandemic versus patients that had their results already reported before this date.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
CCI			

As this IA is unplanned, no alpha spending was planned to control for overall type-I-error inflation and no stopping rules or any other modifications to the study are defined with this IA.

In addition, the Interim Analysis will describe the following characteristics of the study population:

- Disposition (Section 10.1) including and up to the cut-off point,
- Summary of visits / MSQoL assessments performed before and after start of COVID-19 pandemic,
- Baseline Characteristics including MS Disease Characteristics and results from the central MRI review for the screening MRI (Section 11),
- Relevant Previous Medication (Section 12),

and will include the following endpoints:

- Change in MSQoL Overall quality of life at the Month 12 Visit compared to Baseline (Section 14.3.1)
- Global satisfaction, Treatment effectiveness, Side effects, and Convenience assessed by TSQM v1.4 at the Month 6 and Month 12 Visit (Section14.3.2),
- Changes in level of disability as measured by EDSS, at the Month 6 and Month 12 Visit compared to Baseline (Section 14.3),
- Relapse reports including and up to the cut-off point (number and percentage of subjects with (qualifying) relapses),
- Occurrences of TEAEs and SAEs as well as Lymphocyte counts including and up to the cut-off point (Section 15).

These characteristics will be summarized descriptively up to Month 12a Visit in the same way as for the final analysis. In addition, all TSQM scores will be analyzed applying the repeated mixed-effects linear regression as specified in Section 14.3.2 (apart from the inclusion of the Visit effect for Month 24). MSQoL and selected disposition and Baseline analyses will be repeated by subgroup "Month 12 MSQoL assessment after start of COVID-19 pandemic".

Table 2 lists all assessments which will be included in the 1-year interim analysis.

Table 2: List of assessments included in the 1-year interim analysis

Assessments	Screening	Baseline	Month 2	Month 6	Month 12a
Informed Consent	X				
Demographic	X				
iRT		X			
Disease History	X				
CCI					
MSQoL-54		X			X
MRI	X				
CCI					
Lymphocyte Count	X	X	X	X	X
Treatment Satisfaction (TSQM v1.4)				X	X

Assessments	Screening	Baseline	Month 2	Month 6	Month 12a
Treatment Administration		X			
AEs		X	X	X	X
Treatment and Study Termination		X	X	X	X
Relevant Previous Medication	X	X			

Cut-off date

Only data up to and including the Month 12a Visit of each subject will be analyzed in the IA. Therefore, the cut-off date is defined as the maximum Month 12a Visit date (i.e. date of the last assessment for the Month 12a Visit). For subjects with a missing Month 12a Visit the cut-off date will be 360 days after start of study medication. This includes subjects who discontinued before Day 360.

- Cut-off date (Month 12a Visit done) = Month 12a Visit End Date (i.e. Maximum Month 12a Visit date)
- Cut-off date (Month 12a Visit not done) = Start of study medication + 360 days -1

Any assessments from the Month12b or later Visits will not be included in the IA, however, any events or concomitant medications reported during these visits that have an onset/start date before or at the cut-off date will be included.

All events 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).

All data included in the IA will undergo a data cleaning process, however, as the key data point is an ePRO and no decisions on further study conduct are based on this IA, it is not required to have all data 100% cleaned. The quality of the data will be reviewed during the Data Review Meeting.

Data handling after cut-off date

Data not included in the 12 month IA 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 except for the model of the TSQM v1.4 at Month 6 Visit (Section 0), which will only be done for the interim analysis. The TSQM v1.4 at Month 6 Visit will be included in a repeated model at the final analysis (Section 14.3.2).

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

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 5.5.1: "Subjects with lymphopenia lower that the above-mentioned limit and/or occurrence of the above-mentioned infections, resulting in delay of scheduled second year treatment course beyond 3 months will be excluded from, tertiary or exploratory endpoint analysis."

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.

1-year interim analysis:

A 1-year IA was added during the course of the study without a corresponding protocol amendment.

COVID-19 pandemic:

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

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 from 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. The primary analysis will be repeated on the Treatment Completer Sets and on the ITT, if different, to evaluate

the sensitivity 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 Analysis Sets

Subgroup analyses will be performed on subgroups as defined below.

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.

Unless otherwise indicated, all descriptive statistical analyses will be presented separately for pre-treatment naïve and DMD pre-treated subjects.

Month 12 MSQoL assessment after start of COVID-19 pandemic:

- Yes: Date of Month 12 MSQoL assessment (if missing, Month 12a Visit End Date) after start of COVID-19 pandemic (see Section 9 for definition).
- No: Otherwise.

This subgroup is used in 1-year IA and any ePRO analyses dedicated to 1-year data as specified in the respective sections.

Specific analyses as specified in the respective sections will be repeated for these subgroups.

9 General Specifications for Data Analyses

Treatment groups

The treatment group will be labeled as Mavenclad®.

Significance level

All statistical tests mentioned in this IAP are to be regarded as exploratory. All statistical tests will be performed 2-sided. If confidence intervals are to be calculated, these will be 2-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, 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 of the analysis set of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain Visits percentages will be based on the number of 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.

Definition of change from Baseline

Change from Baseline = Visit value – Baseline value

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

Definition of 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 (if not otherwise specified).

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 protocol Section 7.1.3). 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 the study 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 subjects will be classified as if they 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 if 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 assessment 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 last assessment available. In this case the missing ET visit will be imputed by the unscheduled visit.

If not specified otherwise, the assessments of the ET visit will be mapped to the nearest next 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 completely or partially missing but 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.
- In all other cases the missing onset day or missing onset month will be replaced by 1.

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

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

Where tables are presented over time, the total of missing and non-missing observations at each 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 in case of major PDs

Electronic Patient Reported Outcomes (ePRO) assessments performed completely in non-native language will not be used for the statistical summaries or analyses as planned in this IAP and will be flagged accordingly in any listings.

Any other PD will not be considered in the planned statistical analyses.

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:

1. Age will be estimated from the year of birth (year of IC – year of birth), as recorded in the electronic Case Report Form (eCRF)

2. If year of birth is missing, age will be imputed by the mean age of the FAS.

- **Pooled centers**

Some centers will have few eligible subjects only. Therefore, the centers will be pooled together in geographical groups by country and the Scandinavian countries will be further pooled together to one Scandinavian pool.

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 discontinuations. 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 one dose of study medication,
  - who discontinued the study medication, grouped by main reason (reason from last treatment stopped),
  - who discontinued/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
- MSQoL-54 completion status, including reasons for missing data

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.

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

If not stated otherwise, summaries will be presented on the FAS.

11.1 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.
    - Japanese,
        - Yes,
        - No,
        - Missing.
- Age (years)

- Age categories:
  - ≤ 40 years,
  - >40 years, <65 years,
  - ≥65 years,
  - Missing.
- Region:
  - Eastern & Central Europe:
    - (Austria, Hungary, Lithuania, Poland, Slovakia, Czech Republic)
  - Scandinavia:
    - (Denmark, Finland, Norway, Sweden)
  - Southern Europe:
    - (Greece, Italy, Portugal, Spain)
  - Western Europe:
    - (Belgium, France, Netherlands, United Kingdom)
  - Australia
- Pooled Center
  - Defined pooled center.
- Country
  - Country 1
  - …

The following subject data listing will be provided:

- Demographic Data (Country, Sex, Race, Age, EDSS at Baseline, Number of relapses during last year).

11.2 Medical History

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

11.3 Other Baseline Characteristics

MS Disease Characteristics

The duration since onset and diagnosis of MS at Baseline in months, the number of previous DMDs as well as the EDSS at Baseline will be presented. In addition, the number of subjects grouped by the major system 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" (Appendix 1)):
  - 0
  - 1,
  - 2,
  - >2,

MRI Disease Characteristics

The following Screening MRI results will be presented:

- Number of T1-Gd+ enhancing lesions,
- Number of T1-Gd+ enhancing lesions:
  - 0,

  - > 0,
  - Non-evaluable
  - Missing
- Total number of T2 lesions,
- Total number of T2 lesions:
  - 0,
  - 1 - 8,
  - ≥ 9
  - Non-evaluable
  - Missing
- Total T2 lesion volume (cm^3),
- Brain volume (cm^3),
- Grey matter volume (cm^3),
- White matter volume (cm^3),
- Deep grey matter volume (cm^3).

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 $\geq$ 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 of the same month when the IC was provided. If the month is missing as well or the date is completely missing the end date will not be replaced and it will be 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.

13 Treatment Compliance and Exposure

Two years of treatment are planned in this study. Subjects will take tablets in week 1 and week 5 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, 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%
- Missing

The number of planned tablets is based on the weight at the beginning of each treatment course (Table 3).

Table 3: Dose of Mavenclad® per treatment week by subject weight in each treatment year

Weight range	Dose in mg (number tablets) per treatment week	
kg	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 Course 1 Treatment Period and the start of the 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,
- 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 / 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 each 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

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 efficacy endpoints.

For the detailed definition of covariates and stratification factors that are used in the statistical models see Section 9.

Descriptive summary statistics will be presented for the absolute values and the changes from baseline as applicable, for each visit and for all efficacy endpoints for the FAS. Details about the presentation of continuous and qualitative 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: Changes in MSQoL-54 physical and mental health composite scores from Baseline to Month 24 Visit

The primary endpoints are the changes in MSQoL-54 physical and mental health composite scores at Months 24 Visit compared to Baseline.

The MSQoL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument (Vickrey et al., 1995; Vickrey et al., 1997). The MSQoL-54 questionnaire was developed to measure HRQoL in subjects with MS. It is composed of 54 items and is a combination of the SF-36 as well as an additional 18 disease-specific items such as fatigue and cognitive function.

The questionnaires will be summarized in 5 (composite) scores

- Physical health composite,
- Mental health composite,
- Satisfaction with sexual function,
- Change in health,
- Overall quality of life,

which will be derived from the 12 subscales (Physical function, Role limitations-physical, Role limitations-emotional, Pain, Emotional well-being, Energy/fatigue, Health perceptions, Social function, Cognitive function, Health distress, Overall quality of life, Sexual function) following the rules specified in the Scoring Manual (Vickrey 1995). All scores range from 0% to 100%. 100% is the best possible score.

The primary analysis is focusing on the physical and mental health composite scores while the overall quality of life will be analyzed as a tertiary endpoint. The other composite scores and subscales will not be analyzed statistically.

The observed results and changes from Baseline will be tabulated and plotted for Physical health composite, mental health composite and Overall quality of life for the FAS. In addition, the estimated Least Square (LS) Means of the change from Baseline with the corresponding standard error, 95% confidence interval and two-sided p-value of the analysis model (see Section 14.1.1) will be summarized and plotted.

The Overall quality of life, Physical and Mental health composite scores and the change from Baseline of the MSQoL-54 will be listed by subject.

14.1.1 Primary Objective: Analysis of the primary endpoints

The primary objective is to assess the HRQoL through the MSQoL-54 scale in highly active RMS subjects treated with Mavenclad® for 2 years (24 months).

The primary endpoints for the study are the changes in HRQoL assessed by MSQoL-54 physical health and mental health at 24 months post-Baseline assessment. Differences in MSQoL-54 scores between measurements at the Month 24 Visit and Baseline will be assessed using repeated mixed-effects linear regression, accounting for clinically relevant factors, within subject correlation and within pooled center correlation.

As the analysis set concerns repeated measurements for outcomes for each individual, it is likely that observations pertaining to each individual will be correlated. Furthermore, as this is a multi-center study, it is likely that clustering of individuals within study sites will produce an additional source of correlation. Mixed-effects regression, whereby a three-level hierarchical model is specified for observations within subjects within-pooled centers, will be used to account for within-subject and within-pooled center correlation (Gibbons et al., 2010).

The analysis will also adjust for factors deemed to be prognostic for the primary endpoint, as judged by clinical experts. These factors are the age and EDSS at Baseline, (see Section 9 for details).

The primary endpoints are the changes from Baseline to Month 24 Visit in Physical and Mental health composite of the MSQoL-54. They will be analyzed with a repeated mixed-effects linear model for change from Baseline that will take all planned intermediate measurements into account whereby a three-level (visits within subjects within centers) hierarchical model is specified for repeated MSQoL-54 Physical or Mental health composite scores.

$$Y = X\beta + \gamma + e, \text{ where}$$

Y represents change from baseline in MSQoL score,
X represents values of fixed effects including MSQoL score, age and EDSS at Baseline, and Visit (defined as a class variable),
β represents set of regression coefficients,
γ represents pooled center random effect,
e represents a random error, potentially correlated for different visits within a subject (nested within a center).

The LS Means will be calculated with observed margin which reflects the distribution of age, [redacted] categories at Baseline and respective Baseline composite score 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 center effect will be specified as a fixed effect instead (same model as specified as a sensitivity analysis below).

The following hypotheses will be evaluated exploratively:

H_{01}: $\Delta_{\text{Physical Health}} = 0$ vs. H_{11}: $\Delta_{\text{Physical Health}} \neq 0$

H_{02}: $\Delta_{\text{Mental Health}} = 0$ vs. H_{12}: $\Delta_{\text{Mental Health}} \neq 0$,

where $\Delta = EY$ denotes the population mean change of the respective score.

The study is exploratory in nature. A control of the potential type-I-error inflation caused by multiple endpoints and multiple testing is not implemented.

Analysis (Analysis Set)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Changes in MSQoL-54 physical and mental health composite scores from Baseline to Month 24			
Primary (FAS)	Changes from Baseline in physical health composite (MSQoL-54) to the Month 12 Visit and Month 24 Visit	Repeated mixed-effects linear model with the following adjusting factors: • Baseline score, • Age (years), • EDSS (≤3, > 3), • Visit, • Within-pooled center correlations, • 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 that are not adjusted for multiple testing due to the exploratory nature of the study.	Missings at Baseline: Subjects with a missing MSQoL assessment at Baseline will not be included in the repeated mixed-effect linear model analysis. Missing covariate or stratification information will be imputed as specified in Section 9. 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 missing at random. Missing Sexual function scores: See below.
Primary (FAS)	Changes from Baseline in mental health composite (MSQoL-54) to the Month 12 Visit and Month 24 Visit		

Handling of missing scores in sexual function:

The MSQoL-54 questionnaire has been set-up to allow only skipping of questions 46 - 49 about the Sexual function by selecting "Not applicable" as an answer. If more than one question in this part was answered, the Sexual function score will be calculated according to the scoring manual (Vickrey 1995), i.e. the mean of the answered questions will be used as score. If only one or no question was answered, the Sexual function score will be imputed with the answer of the Satisfaction with sexual function score.


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14.2 Secondary Endpoint: Treatment global satisfaction assessed by TSQM v1.4 at Month 6 Visit (Interim Analysis)

The TSQM v1.4 questionnaire is a generic questionnaire to test treatment satisfaction with domains in Effectiveness, Side Effects, Convenience and Global Satisfaction and has previously been used in MS subjects (Vermersch et al., 2014). The scores will be derived according to the TSQM User Manual Version 1.0. The TSQM v1.4v scores range from 0% to 100%, with 100% being the best possible score.

At the Interim analysis, the Global Satisfaction score at Month 6 Visit will be analyzed without taking the later observations into account. At the final analysis, the Month 6 Visit will be analyzed as tertiary endpoint in a repeated model that includes the Month 12 and 24 Visit (see Section 14.3.2).

Global Satisfaction at Month 6 Visit will be analyzed at the interim analysis with a mixed linear model. The model will be adjusted for age (in years), EDSS at Baseline (≤3, > 3) and within-pooled center correlations. 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.


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All volume changes will be listed by subjects.


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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 but 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.
- 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 (latest version available) preferred term (PT) as event category and MedDRA (latest available version) primary system organ class (SOC) body term as Body System category overall and by subgroups, DMD pre-treated and pre-treatment naïve.

Unless otherwise stated adverse events will be displayed in terms of frequency tables: PT and primary SOC in alphabetical order. Only the highest occurred severity of an TEAE by PT and subjects will be displayed in summary tables by severity.

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

The following overall frequencies of subjects with the corresponding TEAE 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 (any severity, 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 total time at risk, which is defined as a 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. Total time at risk can be expressed also in 100 subject-years.

The exact Poisson 95% confidence intervals for the EAIR are calculated using the relationship between the Poisson and the Chi-square distribution (Ulm, 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 patients with fatigue during the month/ Number of patients with fatigue during the month or still in the study at the end of the month) * 100,
where patients with fatigue during the month are all patients 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 (latest version available). 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 follows:

- 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 considering only subjects with post Baseline laboratory samples: Laboratory tests by NCI-CTCAE 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 (latest version available) 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 summaries will be prepared for vital sign parameters as grouped above considering only subjects with post Baseline values:

- 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

Ulm K. A simple method to calculate the confidence interval of a standardized mortality ratio. American Journal of Epidemiology 1990;131(2):373-375.

VERMERSCH, P. et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. Mult Scler, v. 20, n. 6, p. 705-16, May 2014. ISSN 1477-0970. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/24126064 >.

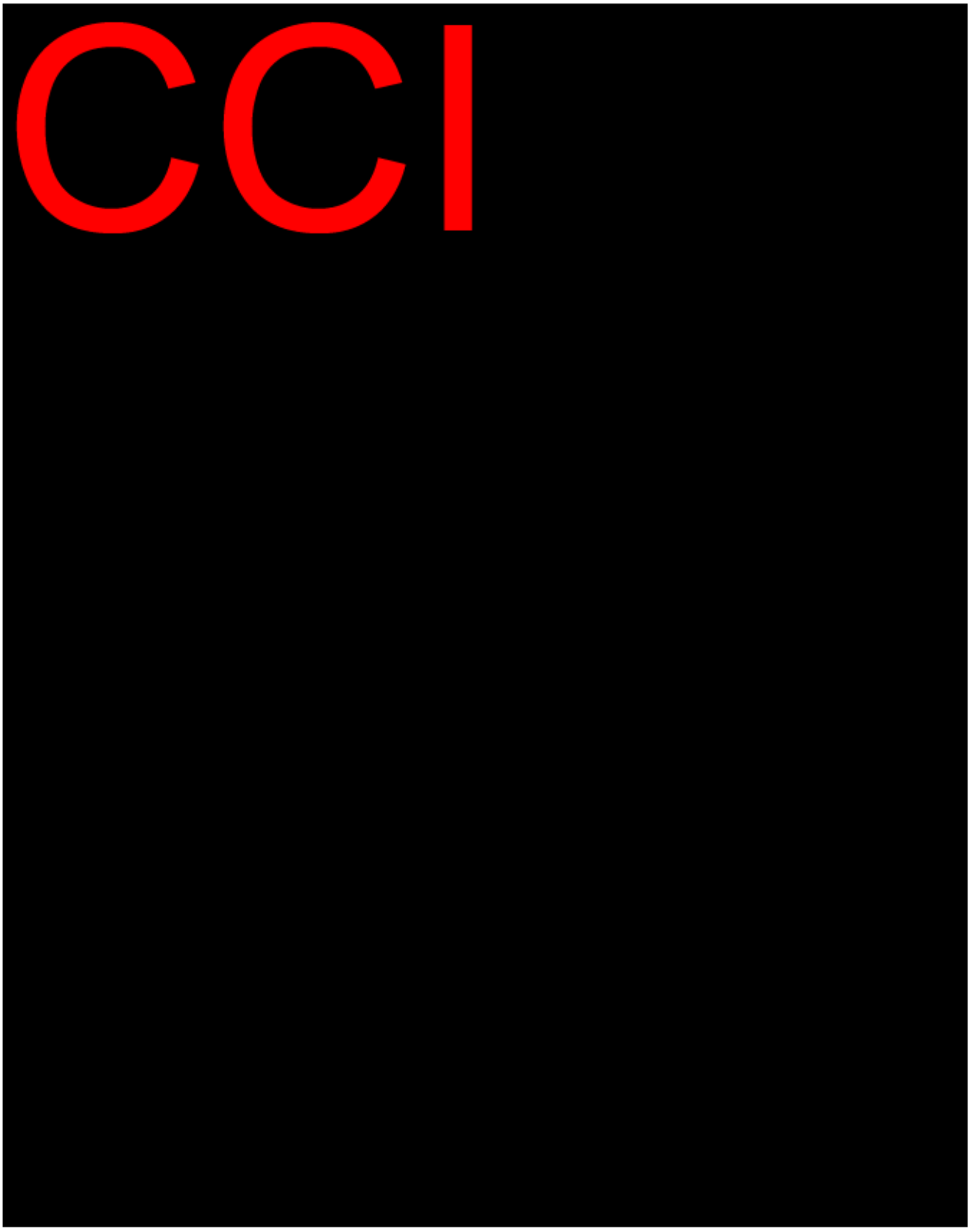
VICKREY, B. G. et al. Comparison of a generic to disease-targeted health-related quality-of-life measures for multiple sclerosis. J Clin Epidemiol, v. 50, n. 5, p. 557-69, May 1997. ISSN 0895-4356. Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/9180648 >.

VICKREY, Barbara G. Multiple sclerosis quality of life (MSQOL)-54 instrument. *Los Angeles: University of California, Los Angeles*, 1995.

QuintilesIMS, User Manual for the Treatment Satisfaction Questionnaire for Medication (TSQM), Version 1.0, July 2017.

Parmenter, B. A., et al. The utility of regression-based norms in interpreting the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J. Int. Neuropsychol. Soc. 16, 6–16 (2010).

18 Appendices



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.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Signature Page for VV-CLIN-279857 v6.0

Approval	PPD 21-Sep-2021 15:07:53 GMT+0000

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