Clinical Trial Protocol

Clinical Trial Protocol Number	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®
Phase	IV
IND Number	Not applicable
EudraCT Number	2017-002632-17
Coordinating Investigator	PPD PPD PPD PPD
Sponsor	Merck KgaA Frankfurter Str. 250 64293 Darmstadt, Germany Medical Responsible: PPD Mobile: PPD
Clinical Trial Protocol Version	14 December 2018 / Version 2.0
Replaces Version	1.0

- Confidential –

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[redacted]

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List of Abbreviations

CCI	
AE	Adverse Event
ALT	Alanine aminotransferase-
ARR	Annualized Relapse Rate
CCI	
BVMT-R	Brief Visuospatial Memory Test - Revised
CMO	Contract Manufacturing Organization
CRF	Case Report Form
CRO	Contract Research Organization
CUL	Combined Unique Lesions
CVLT-II	California Verbal Learning Test – Second edition
DMD	Disease Modifying Drug
eCRF	Electronic Case Report Form
CCI	
EQ-5D	European Quality of Life Five Dimensions Questionnaire
FAS	Full Analysis Set
FS	Functional system
CCI	
GCP	Good Clinical Practice
Gd	Gadolinium
CCI	
HIV	Human Immunodeficiency Virus
HRQoL	Health Related Quality of Life
ICF	Informed Consent Form
ICH	International Council on Harmonisation
ICH GCP	International Council on Harmonisation for Good Clinical Practice
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IPMP	Integrated Project Management Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology

ITT	Intent-To-Treat
CCI	
MCID	Minimally Clinically Important Difference
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSQoL-54	Multiple Sclerosis Quality of Life-54 Questionnaire
CCI	
PML	Progressive Multifocal Leukoencephalopathy
PRO	Patient Reported Outcomes
PY	Patient Years
QoL	Quality of Life
RCT	Randomized Control Trial
RMS	Relapsing Multiple Sclerosis
SAE	Serious Adverse Event
SC	Steering Committee
SDMT	Symbol Digit Modalities Test
SF-36	36-Item Short Form Health Survey
SmPC	Summary of Product Characteristics
CCI	
TEAE	Treatment-Emergent Adverse Event
TB	Tuberculosis
TSQM v1.4	Treatment Satisfaction Questionnaire Medication version 1.4
VZV	Varicella Zoster Virus
WOCBP	Women of Child Bearing Potential

1 Synopsis

Clinical Trial Protocol Number	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
IND Number	Not applicable
FDA covered trial	Not applicable
EudraCT Number	2017-002632-17
Coordinating Investigator	PPD
Sponsor	Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
Sponsor Legal Representative in the European Union	Merck KGaA, Frankfurter Str. 250, 64293 Darmstadt, Germany
Trial centres/countries	Europe (including, but not limited to): Austria, Belgium, Czech Republic, Denmark, Finland, France, Greece, Hungary, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Spain, Slovakia, Sweden, UK, Australia
Planned trial period (first subject in-last subject out)	First Subject First Visit: Q2/2018 Last Subject Last Visit: Q4/2021
Trial Registry	EU Clinical Trials Register ClinicalTrials.gov

Objectives:

Primary:

- 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)

Secondary:

- To assess treatment satisfaction through the TSQM v1.4 questionnaire in highly active RMS subjects at 6 months of treatment with Mavenclad®

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Methodology: This will be an open label, single arm, exploratory, multicentre, 2-year Phase IV study.

Subjects will attend visits for assessments at Baseline and at Months 6, 12, 18, and 24.

Subjects will attend visits for lymphocyte count as per mandatory monitoring at Screening, Baseline and at Months 2, 6, 12, 14, 18 and 24.

Planned number of subjects: 445

Primary endpoint:

- Changes in MSQoL-54 at 24 months compared to Baseline, i.e., the changes in the physical and mental health composite scores

Secondary endpoints:

- Treatment global satisfaction assessed by TSQM v1.4 at 6 months

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Pharmacokinetics: Not applicable

Safety assessments

Safety assessments will include physical examination, including vital signs, routine laboratory tests, and reporting of adverse events (AEs) and SAEs.

Diagnosis and key inclusion and exclusion criteria:

Key inclusion criteria

- Male or female subjects ≥ 18 years old
- Highly active RMS as defined by:
  - One relapse in the previous year and at least 1 T1 Gadolinium (Gd)+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs (DMDs)
  - Two or more relapses in the previous year, whether on DMD treatment or not
- EDSS score ≤ 5.0

Key exclusion criteria:

- Positive test for hepatitis C or positive tests for hepatitis B infection: either hepatitis B surface antigen (HBsAg) positive, or positive hepatitis B core antibody (total anti-HBcAb) confirmed by a positive viral polymerase chain reaction (PCR)
- Current or previous history of immune deficiency disorders including a positive human immunodeficiency virus (HIV) result
- Currently receiving immunosuppressive or myelosuppressive therapy (e.g., monoclonal antibodies, methotrexate, cyclophosphamide, cyclosporine, mitoxantrone or azathioprine), or chronic use of corticosteroids
- History of tuberculosis, presence of active tuberculosis, or latent tuberculosis
- Presence of signs of progressive multifocal leukoencephalopathy (PML) detected by MRI, clinical and/or biomarker evaluations or other (than MS) major Central Nervous System disease clinically diagnosed or evidenced in screening MRIActive malignancy

Investigational Medicinal Product: dose/mode of administration/ dosing schedule:

Mavenclad®, 3.5 mg/kg divided in 2 yearly treatment courses. Each course of treatment consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a subject receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight.

Reference therapy: dose/mode of administration/dosing schedule: Not applicable.

Planned trial and treatment duration per subject: Two years treatment per subject.

Statistical methods:

Differences in MSQoL-54 physical health and mental health composite scores between the Baseline assessment and the 24-month assessment will be evaluated with mixed-effects linear regression, accounting for within-subject correlation and within-centre/region correlation through a hierarchical model. The model will include all available assessment data up to and including the 24-month assessment and consider time as a categorical covariate. The Full Analysis Set (FAS) will be the primary population. Secondary and tertiary endpoints will be assessed using similar methods. Treatment satisfaction assessed by TSQM v1.4 at 6 months will be evaluated during an interim analysis that will be performed as soon as all enrolled subjects reach 6 months after treatment initiation. The analysis at 6 months will be considered as supportive of the 24 months analysis (main analysis).

Safety analysis:

All safety assessments will be descriptively summarized.

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor of this clinical trial with Mavenclad® is Merck KGaA, Frankfurter Strasse 250, 64293 Darmstadt, Germany.

The trial will be conducted at approximately 120 sites across Europe including Austria, Belgium, Czech Republic, Denmark, Finland France, Greece, Hungary, Italy, Lithuania, Netherlands, Norway, Poland, Portugal, Spain, Slovakia, Sweden, UK, as well as in Australia. The study is open to other countries if there appears a need to increase the recruitment.

The Coordinating Investigator, PPD represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonisation (ICH) Topic E6 Good Clinical Practice (ICH GCP). The Coordinating Investigator will provide expert medical input and advice relating to trial design and execution and is responsible for the review and signoff of the clinical trial report.

Signature pages for the Protocol Lead and the Coordinating Investigator as well as a list of Sponsor responsible persons are in Section 12.14.

The trial will appear in the following clinical trial registries: ClinicalTrials.gov, EU Clinical Trials Register and national registries as per local regulations.

A contract research organization (CRO), PPD will undertake the operational aspects of this trial with oversight by the Sponsor. Details of such structures and associated procedures will be defined in a separate Integrated Project Management Plan (IPMP).

The IPMP will be prepared by the CRO. Clinical quality assurance will be performed under the responsibility of the Development Quality Assurance department at Merck KGaA Darmstadt.

The investigational medicinal products (IMP) will be supplied by the Clinical Trial Supply Department of the Sponsor and packaged and labeled by CCI

Details of structures and associated procedures will be defined in a separate Manual of Operations, which will be prepared under the supervision of the Clinical Trial Leader.

3 Background Information

3.1 Multiple Sclerosis

Multiple sclerosis (MS) is a chronic, inflammatory, progressive, demyelinating disease of the central nervous system and is the most common cause of serious neurological disability in young adults (Przybek et al., 2015). The disease course of MS is heterogeneous and unpredictable requiring chronic treatment and regular medical monitoring by numerous methods such as for example, magnetic resonance imaging (MRI) that was designed for the investigation, diagnosis and management of subjects with MS (Oreja-Guevara e Paradig, 2015).

Some subjects experience a highly active disease course with rapid and early disability often heralded by high relapse rates and early motor, cerebellar and/or cognitive dysfunction (Hirst CL et al, 2008).

Early initiation of effective immunotherapy is considered to be important in this group of subjects in order to prevent aggressive disease progression and severe disability accumulation (Dubey D et al, 2016).

3.2 Cladribine Tablets (Mavenclad®) 3.5/kg

Despite the recent approvals of several newer therapies, the treatment burden of MS remains significant. The evidence for the effects of new therapies are weak and often of a short-term nature with little follow up of original trial participants (Tramacare et al., 2015).

It has been demonstrated that treatment with Cladribine Tablets in 2 short courses over 2 consecutive years has consistently shown robust clinically and statistically significant benefits in subjects across the spectrum of Relapsing Remitting Multiple Sclerosis (RRMS) (early to late stages, treatment naïve or experienced subjects) (Giovannoni et al., 2010; Leist et al., 2014). In particular, it was found that treatment with oral Cladribine Tablets resulted in significant improvements in clinical and radiological efficacy outcomes, with significantly more subjects remaining free from relapse, free from 3-month sustained Expanded Disability Status Scale (EDSS) progression and free from MRI lesion activity over 96 weeks compared to placebo (Giovannoni et al., 2010).

Efficacy data from the CLARITY trial showed statistically significant improvements in the annualized relapse rate (ARR), proportion of subjects relapse-free over 96 weeks, proportion of subjects free of sustained disability over 96 weeks and time to 3-month EDSS progression in subject receiving cladribine 3.5 mg/kg compared to subjects on placebo. In addition, cladribine was statistically significantly superior to placebo with regard to number and relative reduction of T1 Gadolinium (Gd)+ lesions, active T2 lesions, and combined unique lesions (CUL) as demonstrated in brain MRI over the entire 96 weeks of the trial.

Mavenclad® is approved (European Medicines Agency approval on 25 August 2017) for the treatment of adult subjects with highly active relapsing MS as defined by clinical or imaging features:

- subjects with 1 relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other disease modifying drugs (DMDs),
- subjects with 2 or more relapses in the previous year, whether on DMD treatment or not

3.3 Safety and Tolerability of Mavenclad®

The safety profile of Mavenclad® has been assessed in depth based on data from all studies of cladribine in MS, including the long-term safety follow-up registry, and post-marketing data sources. Mavenclad®, when administered as monotherapy at a cumulative dose of 3.5 mg/kg over 2 years, was well tolerated and demonstrated a manageable safety profile.

The comprehensive assessment of the safety data has accumulated more than 8500 patient years (PY) of Mavenclad® exposure with up to 8 years of follow-up in Mavenclad®-treated subjects and thus provides additional confidence of the safety profile of Mavenclad®.

The important identified risks associated with Mavenclad® are severe lymphopenia, which is associated with the mechanism of action of the drug, herpes zoster, and tuberculosis. Based primarily

on the mechanism of action of Mavenclad® 5 important potential risks have been identified: severe infections, progressive multifocal leukoencephalopathy (PML), opportunistic infections (other than tuberculosis and PML), malignancies, and teratogenicity/adverse pregnancy outcomes. The Sponsor will follow the proposed risk minimization measures specified in the summary of product characteristics (SmPC) of Mavenclad®.

3.4 Benefit -Risk Assessment

The studies highlighted in Section 3.2 have provided information on the efficacy and safety of Mavenclad®. As reflected in the Mavenclad® SmPC, appropriate risk mitigation measures will be followed for identified and potential risks Mavenclad® in the participating subjects.

The benefit-risk relationship was carefully considered in the planning of the trial. Based on the clinical and safety data available, the Sponsor considers that Mavenclad® has a positive benefit-risk profile that supports its use in this subject group as specified in this clinical trial protocol. The trial will be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship and would render continuation of the trial unethical.

Based on the available nonclinical and clinical data to date, the conduct of the trial specified in this protocol is considered justifiable.

3.5 Scientific Rationale for Trial Design

3.5.1 Quality of life and Treatment Satisfaction

The relapsing form of MS is characterized by episodes of neurological deterioration (Vollmer, 2007; Trapp e Nave, 2008) requiring increased medical care and sometimes hospitalization (Morrow, 2007; Oleen-Burkey et al., 2012; Maurer et al., 2016). Studies have linked the number of recurring relapses with disability progression (O'connor et al., 2011) and impacting systems such as motor function and cognition (Arroyo Gonzalez et al., 2016). The accumulation and worsening of disabilities over time disrupts subjects' family, social, and working life, undermining their capacity to function in society and tangibly diminishing their HRQoL (Jones et al., 2016).

The quality of life (QoL) of subjects with MS is lower than subjects with any other chronic conditions, including ischemic heart disease, type-2 diabetes, and Crohn's disease (Orme et al., 2007). This is further exacerbated by increased relapse frequency and progression of disease (Parkin et al., 2000; Baumstarck et al., 2015).

HRQoL can be impacted in many different ways. The burden of disability and comorbidities experienced by subjects with MS has a detrimental effect on QoL (Grytten et al., 2012, Aymerich et al., 2009, Orme et al., 2007). Both progression of disability and frequency of relapse contribute to worsening of QoL (Parkin et al., 2000; Baumstarck et al., 2015). The presence of a relapse can be associated with reduced QoL in emotional, mental health, and social function domains compared with subject who had not experienced a relapse (Parkin et al., 2000). Relapses have been found to worsen fatigue (Maurer et al., 2016) which is a predominant symptom for MS subjects. Higher levels of fatigue are not only concomitant with greater impairments in functional mobility and physical

HRQoL, but also have a mutually intertwined relationship with cognition, depression, and mental health (Garg et al., 2016).

Mavenclad® is a drug given orally with a unique posology of maximum 20 days of treatment in two years. The safety monitoring is not frequent, due to the highly selective mechanism of action that targets specifically the mature immune system. In such a context, MSQol-54 is probably an ideal questionnaire. It can address the impact of such a low burden treatment in overall quality of life, in a study where functional scales are also used for fatigue, depression and anxiety and Multiple Sclerosis Functional Composite (MSFC) assessments like CCI [redacted] are included.

TSQM v1.4 questionnaire is a simple, non-MS specific, but the most widely used treatment satisfaction questionnaire in MS. It has not been used in pivotal Cladribine Tablets trials.

Whilst the Mavenclad® randomized control trials (RCTs) provide a wealth of information on clinical and safety outcomes, effects for HRQoL, cognition, treatment satisfaction, and employment status need to be further explored. In CLARITY trial MSQoL-54 and EQ-5D scales were used and outcomes were analyzed, but no clear differences in terms of responsiveness between the randomized subject groups (those treated with Mavenclad® and those treated with placebo) were evidenced. A possible explanation for this could be the fact that subjects entering the trial had already high HRQoL levels. However, subjects enrolled in the CLARITY trial were not diagnosed with high disease activity RMS, as defined in the inclusion criteria of the present trial.

3.5.2 Cognition and Correlation with Brain Atrophy

The effect of MS upon cognition is also significant. Cognitive impairment can affect subjects at all stages, but it is challenging to clinically assess this impact (Langdon et al., 2012). They can include loss of memory functions and processing speed or impact executive functions making daily life a challenge (Muckschel et al., 2016). Subjects have reported that cognitive impairments can have a greater negative impact on their HRQoL than their physical symptoms (Penner, 2016). Cognition therefore carries a significant disease burden.

Brain atrophy has been linked to cognitive impairment in previous studies (Amato et al., 2013, Mineev et al., 2009, and Houtchens et al., 2007). The Symbol Digit Modalities Test (SDMT) (a Brief International Cognitive Assessment for Multiple Sclerosis [BICAMS] component) has been correlated to Deep Gray Matter volume (Batista et al., 2011).

This study is an opportunity to collect large scale data on both BICAMS, a MS specific neuropsychologic test and MRI lesions before and after Mavenclad® administration.

3.5.3 Other Functional Scales

Apart from cognitive problems such as in memory and attention, other factors contributing to QoL worsening are depression and fatigue (Flensner et al., 2013). Approximately 60 to 80% of subjects with MS experience fatigue, which has been described as distinct from any prior experience of feeling tired (Flensner et al., 2013). Fatigue was found to significantly worsen QoL and capacity to work (Flensner et al., 2013).

A large number of subjects with MS (55-58%) are unable to retain employment following diagnosis (Julian et al., 2008; Bøe Lunde et al., 2014).

Lower productivity engenders a reduced sense of autonomy and financial pressures due to reduced income which negatively impacts the subject and the wider economy (Jones et al., 2016).

4 Trial Objectives

4.1 Primary Objective

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

4.1.1 Primary Endpoint

- Changes in MSQoL-54 at 24 months compared to Baseline, i.e., the changes in the physical and mental health composite scores

4.2 Secondary Objective

To assess treatment satisfaction through the TSQM v1.4 questionnaire in highly active RMS subjects at 6 months of treatment with Mavenclad®

4.2.1 Secondary Endpoint

- Treatment global satisfaction assessed by TSQM v1.4 at 6 months

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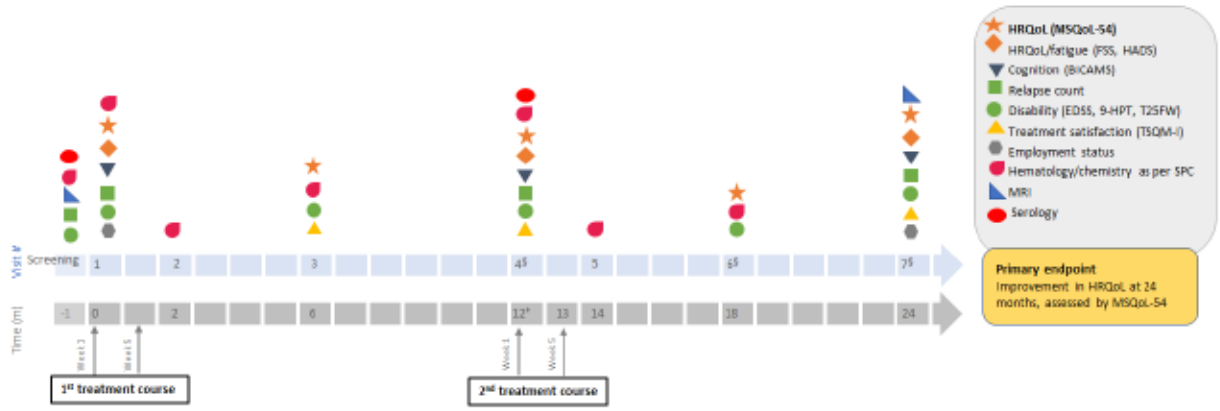
5 Investigational Plan

5.1 Overall Trial Design and Plan

A schematic of the trial design is presented in Figure 1.

Figure 2: Schematic of the Trial Design



† Second treatment course may be delayed for some subjects (see Section 5.5.1). § 0–3 month window for these trial visits.

5.2 Discussion of Trial Design

This will be a single arm, open label, multicentre, 24-month Phase IV trial. Subjects with RMS will receive Mavenclad® 3.5 mg/kg body weight over two years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course will consist of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective year. There will be a 3-month window allowance for subjects for whom the second year course delays (5.4.1 and 5.5.1)

At *screening*, all subjects will have a pre-Baseline MRI scan as well as tuberculosis (TB; active and latent) and serology tests within the month leading up to the Baseline visit in order to support the diagnosis of highly active RMS and ensure compliance with inclusion and exclusion criteria.

Re-screening will be allowed once for those subjects who do not meet the inclusion/exclusion criteria within the above specified time limits. The Medical Monitor must promptly inform the Sponsor about requests and reasons for re-screening.

Baseline is defined as the day on which the first dose of Mavenclad® is administered. All Baseline assessment should take place before Mavenclad® administration.

Subjects will attend visits for assessments at Baseline, Month 6, 12, 14, 18, and 24. A time window of up to 3 months will be allowed for the visits following the second course (see also Section 7).

Subjects will attend visits for lymphocyte count as per mandatory monitoring at Screening, Baseline and at Months 2, 6, 12, 14, 18 and 24.

Subjects who discontinue Mavenclad®at any time during the trial will continue to participate in the scheduled visit for safety assessments and mandatory monitoring. In the event of early discontinuation from the trial, the subject should return for the Early Termination visit for final assessment.

Visit schedules for efficacy and safety assessments are detailed in Appendix 1: Schedule of Assessments.

5.2.1 Inclusion of Special Populations

Not applicable.

5.2.2 Steering Committee

A Steering Committee (SC) has been established; the Steering Committee Charter will be in place that describes the SC responsibilities.

The SC is a multidisciplinary group of lead trial Investigators, medical experts, and Sponsor's personnel, who, collectively, have the scientific, medical, and clinical trial management experience to design, conduct and evaluate the trial.

The SC provides advice and recommendations with regard to the design, the conduct, and the evaluation of the trial.

The SC is responsible for safeguarding the interests of participating subjects and for the conduct of the trial.

5.3 Selection of Trial Population

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject or the subject's legal representative has provided written informed consent following the procedure described in Section 9.2.

5.3.1 Inclusion Criteria

To be eligible for inclusion into this study, the subjects must fulfill all of the following criteria:

1. Subjects must voluntarily give written informed consent. Subjects must read and fully understand the Informed Consent Form (ICF) and the requirements of the trial and must be willing to comply with all trial visits and assessments
2. Male or female subjects ≥ 18 years old
3. Highly active relapsing MS as defined by:
   - One relapse in the previous year and at least 1 T1 Gd+ lesion or 9 or more T2 lesions, while on therapy with other DMDs
   - Two or more relapses in the previous year, whether on DMD treatment or not
4. EDSS score ≤5.0
5. Female subjects of child-bearing potential must use highly effective methods of contraception to prevent pregnancy for 4 weeks before initiation of Mavenclad® and must agree to continue to practice adequate contraception for at least 6 months after the last dose (See Appendix 15 for the list of Highly Effective Birth Control Method. A woman is considered of child-bearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Women using systemically acting hormonal contraceptives should add a barrier method during Mavenclad® treatment and for at least 4 weeks after the last dose in each treatment year. WOCBP must not be pregnant nor lactating, or breast-feeding at Screening through at least 1 week after the last dose
6. Male subjects must be willing to use a condom in addition to having their female partner use another form of contraception (such as an intra-uterine device [IUD], barrier method with spermicide, or hormonal contraceptive [e.g., implant, injectable, patch or oral]) from Baseline

until 6 months after the last dose of Mavenclad®, unless their partners are infertile or surgically sterile

7. Subjects who test positive for Varicella Zoster virus (VZV) will be included. In case of negative serology, the subject may be included after 4 to 6 weeks of receiving VZV vaccination

5.3.2 Exclusion Criteria

To be eligible for inclusion in this study the subjects must not meet any of the following criteria:

1. Hypersensitivity to Mavenclad® or to any of the excipients listed in the SmPC
2. Lymphocyte count not within normal limits of the local, hospital laboratory before initiation of first treatment course
3. Presence of signs of PML detected by MRI, clinical and/or biomarker evaluations or other (than MS) major Central Nervous System disease clinically diagnosed or evidenced in screening MRI
4. Positive for Human Immunodeficiency Virus (HIV),
5. Positive hepatitis C or positive tests for hepatitis B infection: either hepatitis B surface antigen (HBsAg) positive, or positive hepatitis B core antibody (total anti HBcAb) confirmed by a positive viral polymerase chain reaction (PCR). An individual benefit-risk evaluation should be performed before initiating Mavenclad® in non-immune subjects for Hepatitis B and the individual level of risk for HBV infection should be assessed by the Investigator
6. History of active tuberculosis (TB), current diagnosis of active tuberculosis, undergoing current treatment for latent TB infection (LTBI), LTBI as detected by local standard of practise like imaging (e.g., chest X-ray, chest computerized tomography [CT] scan, MRI) and/or positive QuantiFERON-TB Gold test and/or skin test and/or clinical examination
7. Immunocompromised subjects, including subjects currently receiving immunosuppressive or myelosuppressive therapy with, e.g., monoclonal antibodies, methotrexate, cyclophosphamide, cyclosporine, mitoxantrone or azathioprine, or chronic use of corticosteroids
8. Active malignancy. An individual benefit-risk evaluation should be performed before initiating Mavenclad® in subjects with prior malignancy. Subjects treated with Mavenclad® should be advised to follow standard cancer screening guidelines
9. Subjects with hereditary problems of fructose intolerance
10. Subjects having received a live vaccine within 4 to 6 weeks prior to Mavenclad® administration or intends to receive a live vaccination during the trial. After the last dose of Mavenclad®, the subject should avoid live vaccine as long as the subject's white blood cell counts are not within normal limits
11. Allergy or hypersensitivity to Gd and/or any other contraindication to perform an MRI
12. Moderate or severe renal impairment confirmed as per the standards of local clinical practice (for example, creatinine clearance <60 mL/min)
13. Moderate or severe hepatic impairment confirmed as per the standards of local clinical practice (for example, Child-Pugh score >6)
14. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the trial

5.4 Criteria for Initiation of Trial Treatment

5.4.1 Criteria for Initiating and Continuing Therapy

Lymphocyte counts must be:

- Normal before initiating Mavenclad® in year 1,
- At least 800 cells/mm³ before initiating Mavenclad® in year 2.

5.5 Criteria for Subject Withdrawal

Subjects will be informed that they have the right to withdraw from the trial at any time, without prejudice to their medical care, and that they are not obliged to state their reasons. Any withdrawal must be fully documented in the electronic case report form (eCRF) and source documents, and should be followed up by the Investigator.

5.5.1 Withdrawal from Trial Therapy

Withdrawal may *be considered* in the following cases:

- Any subject that does not fulfill the above mentioned criteria (Section 5.4) for the first and/or the second course of treatment
- Occurrence of infection such as herpes zoster, latent hepatitis or latent tuberculosis. In this case adequate anti-infection treatment should be initiated and withdrawal from or delay of second course of Mavenclad® should be considered

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. However, these subjects will receive the second treatment course once the lymphocyte count is appropriate and/ or infection is resolved. Data from these subjects will be reported as an addendum to the final trial report. If recovery from lymphopenia and/or infectious disease takes more than 6 months, the subject should not receive the second treatment course of Mavenclad®.

Withdrawal is *mandatory* in the following cases:

- Withdrawal of consent
- Protocol violation, including non-compliance that in the opinion of the Investigator or Sponsor necessitates the subject being removed. The decision to withdraw the subject should be taken in consultation with the Medical Monitor
- Pregnancy
- Initiation of treatment with an experimental drug
- Initiation of treatment with another disease modifying therapy for MS
- Occurrence of active malignancies
- Evidence or suspect of PML
- Occurrence of an exclusion criterion that is clinically relevant and affects the subject's safety, if discontinuation is considered necessary by the Investigator and/or Sponsor

- Lymphocyte count less than 800 cells/mm³ for more than 6 months before initiation of second treatment course
- Live or live attenuated vaccine at any time during the trial duration
- Any events that unacceptably endanger the safety of the subject

If a subject is lost to follow-up, every possible effort must be made by trial centre personnel to contact the subject and determine the reason for discontinuation. The measures taken to follow-up must be documented. If a subject discontinues before completion of trial procedures, the reason for discontinuation must be documented in the case report form (CRF) and source documents.

Subjects who discontinue Mavenclad® at any time during the trial will continue to participate in the scheduled visits for assessments until his/her planned trial completion. In the event of early discontinuation from the trial, the subject should return for the Early Termination visit for final assessment.

Withdrawn subjects will not be replaced.

5.5.2 Withdrawal from the Trial

Subjects may withdraw from the trial at any time without giving a reason. Withdrawal of consent will be considered withdrawal from the trial. The Investigator should make every attempt to clarify the level of withdrawal: e.g., whether or not data collected can be evaluated, banked samples can still be retained and evaluated, if the subject can still be contacted by phone for checking his/her status (e.g., alive or not), or to return for scheduled visits. In case of withdrawal from the trial for reasons other than consent withdrawal, the assessments scheduled for the Early Termination visit should be performed immediately. In any case, the appropriate eCRF section must be completed. Subject will be asked to confirm that any samples collected but not yet analyzed can be utilized.

Subjects withdrawn from trial medication will continue the scheduled assessments until his/her planned trial completion. These subjects will be managed based on the Investigator's clinical judgment and per local guidelines, and any new medication prescribed in such a period will be recorded. In any case, the appropriate eCRF section must be completed.

The Investigator may withdraw a subject at any time if this is considered to be in the subject's best interest.

5.6 Premature Termination of the Trial

The clinical trial may be terminated prematurely or suspended at the request of Health Authorities or if new safety or efficacy information leads to an unfavorable risk benefit judgment for the IMP. The Sponsor may discontinue the trial if it becomes unjustifiable for medical or ethical reasons, for poor enrollment, or because of discontinuation of clinical development of the IMP or withdrawal of the IMP or comparator from the market for safety reasons.

Health Authorities and Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) will be informed about the discontinuation of the trial in accordance with applicable regulations.

5.7 Definition of End of Trial

The end of the trial is defined as the last subject's End of Trial visit.

5.8 Planned Extension Studies

Upon completion of trial, subjects will be offered the opportunity of enrolling into an Extension trial that may be planned by the Sponsor, for a further 2 years (until 4 years plus the allowance windows from first treatment year course). A separate protocol will be followed for the Extension trial. For all subjects who for any reason do not enter the Extension trial, all their data will be used for the analysis in the Extension trial, given that consent is obtained for these subjects.

6 Investigational Medicinal Product and Other Drugs Used in the Trial

The term "Investigational Medicinal Product" refers to the active substance cladribine being tested in this trial.

IMP provision to the site is automated and is triggered by the Site Activation in interactive response technology (IRT). Following resupplies are controlled by IRT algorithms and are also automated. IMP dispensation to the patients is done through IRT web interface when Baseline and Month 12 visits are registered in the system.

6.1 Description of the Investigational Medicinal Product

The IMP is oral cladribine (INN name) / Mavenclad®10 mg tablets (tradename).

Mavenclad® 10 mg tablets are white, round, biconvex tablets of 8.5 mm diameter, engraved with 'C' on one side and '10' on the other side.

The tablets contain the following excipients: CCI [redacted]

6.2 Dosage and Administration

6.2.1 Posology

The recommended cumulative dose of Mavenclad® is 3.5 mg/kg body weight over 2 years, administered as 1 treatment course of 1.75 mg/kg per year. Each treatment course consists of 2 treatment weeks, one at the beginning of the first month and one at the beginning of the second month of the respective treatment year. Each treatment week consists of 4 or 5 days on which a subject receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. Following completion of the 2 treatment courses, no further Mavenclad® treatment is required in years 3 and 4.

6.2.2 Distribution of Dose

The distribution of the total dose over the 2 years of treatment is provided in Table 1. For some weight ranges the number of tablets may vary from one treatment week to the next. Use of oral Mavenclad® in subjects weighing less than 40 kg has not been investigated.

Table 1: Dose of Mavenclad® per treatment week by subject weight in each treatment year

Weight range	Dose in mg (number of 10 mg tablets) per treatment week	
kg	Treatment week 1	Treatment week 2
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)

Table 2 shows how the total number of tablets per treatment week is distributed over the individual days. It is recommended that the daily Mavenclad® doses in each treatment week be taken at intervals of 24 hours at approximately the same time each day. If a daily dose consists of two tablets, both tablets are taken together as a single dose.

Table 2: Mavenclad® 10 mg tablets per week day

Total number of tablets per week	Day 1	Day 2	Day 3	Day 4	Day 5
4	1	1	1	1	0
5	1	1	1	1	1
6	2	1	1	1	1
7	2	2	1	1	1
8	2	2	2	1	1
9	2	2	2	2	1
10	2	2	2	2	2

A missed dose must be taken as soon as remembered on the same day according to the treatment schedule.

A missed dose must not be taken together with the next scheduled dose on the following day. In the case of a missed dose, the subject must take the missed dose on the following day, and extend the

number of days in that treatment week. If two consecutive doses are missed, the same rule applies, and the number of days in the treatment week is extended by two days.

6.3 Assignment to Treatment Groups

Not applicable.

6.4 Non-investigational Medicinal Products to be Used

Not applicable.

6.5 Concomitant Medications and Therapies

All concomitant medications taken by the subject during the trial, from the date of signature of informed consent are to be recorded in the appropriate section of the CRF, noting the name, dose, duration and indication of each drug. Nondrug interventions and any changes to a concomitant medication or other intervention should also be recorded in the CRF. Any medications that are considered necessary to protect subject welfare and will not interfere with the trial medication may be given at the Investigator's discretion.

The treating physician must consider the following conditions with particular attention, specifically checking the reasons for the administration of a concomitant medication for the cases that follow (see Section 6.5.1).

6.5.1 Permitted Medicines

6.5.1.1 Disease Related

All concomitant medications used for conditions / symptoms related to MS (for example pain, fatigue or weakness, incoordination, bladder dysfunction, spasticity, etc.).

6.5.1.2 Medical History Related

All concomitant medication used for a medical condition already reported in the subject's medical history (for example, any form of pain, especially low back pain and headache, depression, etc.) or family history (primary headache, insomnia, etc.).

6.5.1.3 Self-medication

As this is an outpatient trial, special care will be taken to question subjects on any self-medication and will be asked to respond about the details of the administration of the doses and the concomitant medications in a diary. The use of any herbal or natural product, or other "home remedies" is allowed. However, the use of these products, and the use of vitamins, nutritional supplements and all other concomitant medicinal products should be also noted in a diary.

6.5.1.4 Relapse management

In case of neurological events related to MS, with relapse criteria (Section 7.3.3), treatment with either acute short-term systemic corticosteroids or adrenocorticotropic hormone (ACTH) or plasma exchange can be administered at the discretion of the Investigator, following local good medical practice and international guidelines.

The initiation of Mavenclad® following acute management of relapse will be at the Investigator's discretion. The initiation of the second treatment course can start as soon as the relapse treatment is finished or can be postponed at the Investigator's discretion.

6.5.2 Prohibited Medicines

The following treatments are prohibited:

- Immunosuppressive or myelosuppressive therapy with, e.g., methotrexate, cyclophosphamide, cyclosporine, mitoxantrone or azathioprine, or chronic use of corticosteroids because of a risk of additive effects on the immune system
- Other disease-modifying medicinal products
- Substances that affect the haematological profile (e.g. carbamazepine)
- Vaccination with live or attenuated live vaccines should be avoided during and after Mavenclad® treatment as long as the subject's white blood cell counts are not within normal limits

Follow as per Mavenclad® SmPC.

6.5.3 Other Interventions

Not applicable.

6.5.4 Special Precautions

As per SmPC, special considerations should be taken ahead of the use of particular substances.

6.5.4.1 Switching from Other DMDs

For the subjects switching from another DMD, the mode of action and duration of effect of the current, or previous DMD should be considered prior to initiation of Mavenclad®. In such cases, it is at the Investigator's discretion to define the required time interval between completing the previous treatment and initiating Mavenclad® treatment. This decision must be based upon the respective treatments' European Medicines Agency SmPC*, independently published guidelines (i.e. Kompetenznetz Multiple Sklerose [KKNMS]) and standards of care

* The washout period/ time to wait before switching from one DMD to another, can be described in the product characteristics of the respective drug."

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

Anti-herpes prophylaxis will be provided to subjects with grade 4 lymphopenia. Standard anti-infectious treatment is allowed in case of the occurrence of infection.

6.6 Packaging and Labeling of the Investigational Medicinal Product

Mavenclad® will be supplied in CCI packages, containing one, four and six tablets (to be confirmed by simulation and will for either CCI

All IMPs will be packaged and labeled in accordance with all applicable regulatory requirements and Good Manufacturing Practice Guidelines.

6.7 Preparation, Handling, and Storage of the Investigational Medicinal Product

As the tablets are uncoated, they must be swallowed immediately once removed from the CCI and not be left exposed on surfaces or handled for any period of time greater than that required for dosing. If a tablet is left on a surface or if breaks and fragments fall from the blister, the area must be thoroughly washed. Hands must be dry when handling the tablets and washed thoroughly afterwards.

Store in the original package in order to protect from moisture.

On site, all IMP should be stored in a secure location, in a temperature-controlled environment, preferably with a temperature log maintained daily, and may be dispensed only by the Investigator or by a member of staff specifically authorized by the Investigator, or by a pharmacist, as appropriate. Any deviations from the recommended storage conditions should be immediately reported to the Sponsor and use of the IMP interrupted until the Sponsor has given authorization for its continued use.

6.8 Investigational Medicinal Product Accountability

The Investigator (or designee) is responsible for ensuring IMP accountability, including reconciliation of drugs and maintenance of records.

- Upon receipt of IMP, the responsible person will check for accurate delivery and acknowledge receipt by signing or initialing and dating the appropriate documentation and returning it to the location specified. A copy will be archived for the Investigator Site File.
- IMP dispensing will be recorded on the appropriate drug accountability forms so that accurate records will be available for verification at each monitoring visit.
- Trial site IMP accountability records will include the following:
  - Confirmation of IMP receipt, in good condition and in the defined temperature range.
  - The inventory of IMP provided for the clinical trial and prepared at the site.

- The use of each dose by each subject.
- The disposition (including return, if applicable) of any unused IMP.
- Dates, quantities, batch numbers, box numbers, expiry dates, and the individual subject trial numbers.

The Investigator site should maintain records, which adequately document that subjects were provided the doses specified in this protocol, and all IMPs provided were fully reconciled.

Unused IMP must not be discarded or used for any purpose other than the present trial. No IMP that is dispensed to a subject may be redispensed to a different subject.

A Trial Monitor will periodically collect the IMP accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or designee or authorizing their destruction by the trial site. In the event the site is unable to destroy unused and used containers, it is recommended local or regional destruction is organized by the CRO. Unused and used containers must only be returned to the sponsor Contract Manufacturing Organization (CMO) depot, if required by the local law.

6.9 Assessment of Investigational Medicinal Product Compliance

Subjects should be instructed to bring with them to each visit; both opened and unopened IMP packages, in order to allow the assessment of compliance with trial treatment. IMP administration must be recorded in the eCRF.

Subjects will be provided with subject diary forms to record the dose and time of treatment administration. Subject diary entries should be collected at each trial visit and checked for completeness and accuracy. Subjects should be asked to explain/correct any discrepancies in their diary forms (see Appendix 12: Personal Diary)

6.10 Blinding

Not applicable.

6.11 Emergency Unblinding

Not applicable.

6.12 Treatment of Overdose

An overdose is defined as any dose greater than the highest daily dose included in a clinical trial protocol or planned for an individual subject enrolled in the trial. The determination of an overdose will be left to the discretion of the Investigator, based on the quantity of overdose, emergence of any clinical signs and symptoms suggestive of a toxic administration, as well as his/her own clinical judgment as it applies to each individual case.

There is no known specific antidote to an overdose of the IMP. Treatment consists of careful observation and initiation of appropriate supportive measures. Discontinuation of the IMP may need to be considered. Because of the rapid and extensive intracellular and tissue distribution, hemodialysis is unlikely to eliminate the IMP to a significant extent.

Even if it does not meet other criteria for an SAE, any overdose must be recorded in the IMP section of the eCRF and reported to Drug Safety in an expedited manner by completing the eCRF SAE page, and following the procedure in Section 7.4.

6.13 Medical Care of Subjects after End of Trial

The Sponsor will not provide any additional care to subjects after they leave the trial because such care should not differ from what is normally expected for subjects with RMS.

7 Trial Procedures and Assessments

A schedule of the tests and evaluations to be conducted during the course of this trial is located in Appendix 1: Schedule of Assessments.

Patient reported outcome (PRO) questionnaires must be performed prior to clinical assessments at all visits and prior to Mavenclad® administration for both treatment courses. The order of the assessments is as below:

1. MSQoL-54
2. TSQM v1.4

PROs will be completed on a hand held tablet device, on site at the clinic. PROs will be migrated to an app based solution which allows text and scale questions to be configured to maintain the validity of the assessment. The tablet device used in this trial will be the Apple iPAD Air 2. Participants can ask for assistance in operating the device and accessing the questionnaires. Data collected through the ePRO questionnaires will be stored in the trial electronic data capture (EDC).

Responsible site staff will be trained on MSQoL-54, CCI , TSQM v1.4, CCI before first test implementation to subjects.

Training modules would be useful for the sites about these and other questionnaires for sake of low interrater variability. Whenever possible, the same assessor should manage the same patient for these scales.

In this protocol, symptoms and signs of relapse or worsening of MS since the previous visit will usually be captured in the context of the efficacy assessment, and recorded on the relapse module of the eCRF. Therefore, symptoms, relapses or worsening of MS will not be considered as AEs nor captured on the AE module of the eCRF unless considered possibly or probably related to the IMP (i.e. worsening is not consistent with the anticipated natural progression of the disease).

7.1 Schedule of Assessments

7.1.1 Screening (Month -1 to Baseline)

A complete Screening Evaluation is to be performed up to -1 month before Baseline. Screening will include the following assessments:

- Signing ICF
- Demographic data, including date of birth, gender and race
- Medical history, including concomitant medications and concomitant procedures
- Disease history, including classification of disease, number of relapses within the past 12 months, treatment history, diagnosis date
- Blood samples for serology and safety analysis at local laboratory (see Section 7.4.3)*
- A lymphocyte count*** at local laboratory facilities
- Physical examination, including vital signs (blood pressure, heart rate, temperature)
- MRI assessment (see Section 7.3.5)
- CCI [redacted]
- The contraceptive method used will be recorded, or, alternatively, if applicable, the age at menopause will be captured
- Urine or serum pregnancy test (for WOCBP only) at local laboratory**
- Review of inclusion/exclusion criteria

***If the local laboratory blood test for serology and safety analysis mentioned at Screening visit is conducted within 10 days of the visit, no blood samples need to be repeated at Screening visit.**

****Additional serum or urine pregnancy tests will be permitted throughout the trial period as required by country specific regulations.**

*****Lymphocyte count must be normal before initiating Mavenclad in Year 1.**

Assignment of Subject ID Number:

Once the subject has provided informed consent, the IRT System will be notified which will generate a Subject ID Number in the following format:

(10 Digit Study Number) (3 Digit Site Number) (4 Digit Subject Count at Site starting from 0001).

For example, at site 101, the 5th patient screened in study 7005680021.

Study No.	Site No.	Subject No.
7005680021	101	70056800211010005

Once all procedures and assessments for this visit are completed, an appointment for the Baseline visit (within 1 month from Screening) will be made and the subject will be discharged.

In certain cases, prolongation of screening period is allowed. Examples of such cases are below:

- Requirement of a time interval between completing the previous treatment and initiating Mavenclad® treatment. (see Section 6.5.4.1)
- Requirement of a 4 to 6 week pause after the varicella vaccination

Each case of screening period extension must receive in advance, a written approval from the Medical Monitor.

7.1.2 Rescreening

Subjects who do not meet the inclusion/exclusion criteria within the specified time limits (i.e., 1 month) and screen fail may undergo re-screening once if approved by the Medical Monitor. If the subject is re-screened, the subject will receive a new subject identification number and will be asked to sign a new ICF.

Subjects with test results that do not meet the inclusion/exclusion criteria may have testing repeated once only if the results are thought to represent a laboratory error or a reversible or clinically insignificant intermittent condition. If testing is repeated for such subjects, all screening tests will need to be repeated except for the TB test, human immunodeficiency virus, and hepatitis testing, which may be repeated separately from the other tests as necessary. The Medical Monitor may also give permission for tests to be repeated separate from other tests as necessary. If inclusion/exclusion criteria are not met based on the results of the repeated tests, the subject should be considered a screen failure and not be enrolled in the trial. Repeat tests should be conducted and results available prior to Baseline.

7.1.3 Treatment Period

The treatment period begins with the completion of all Baseline assessments and the initiation of trial drug treatment on Trial Day 1 and continues through to the completion of the treatment period at the Month 24 Visit.

7.1.4 Baseline Visit (Visit 1)

The following procedures and assessments will be performed at this visit:

- Review of inclusion/exclusion criteria
- CCI [redacted]

- CCI
- Urine or Serum pregnancy test (for female subjects of child-bearing potential only)
- Assessment of concomitant medications and concomitant diseases
- A lymphocyte count**, at local laboratory facilities
- HRQoL
  - MSQoL-54
  - CCI
  - CCI
- CCI
- CCI
- Weight measurement and assignment of IMP via IRT
- Administration of trial medication and provision of trial medication intake for Month 2

***If the neurological examination is conducted within 10 days of Baseline and the subject reports no change in status, no neurological examination needs to be repeated on Baseline (Visit 1).**

****If the lymphocyte count has been performed within one month of Baseline, no lymphocyte count needs to be repeated on Baseline.**

Each subject will be given a diary form to record the dose, date and time of each administration of IMP, AEs, concomitant medications and procedures (see Appendix 12: Personal Diary). The subject diary entries must be reviewed by the trial coordinator(s)/nurse(s) with the subject to clarify any discrepancies and ensure proper completion. This review must be completed at each visit and the review recorded in the subject's clinic visit notes. The appointed designee will enter in the eCRF what each subject records on his/her subject form and any information that is obtained after subsequent questioning of the subjects.

Since accurate drug dosing is based on weight, prior to dispensing the treatment medication at Day 1 for treatment course Year 1 and Year 2, the subject's weight should be accurately assessed.

Once all procedures and assessments for this visit are completed, an appointment for the next visit will be made and the subject will be discharged.

7.1.5 Month 2 Visit 2 (±7 days)

Subjects will undergo:

- A lymphocyte count as per mandatory monitoring at local laboratory facilities*
- Review of subject diary
- Assessment of AEs, concomitant medications and concomitant procedures

*Lymphocyte count will be checked locally after 2 months of starting treatment. If the lymphocyte count is below 500 cells/mm³, it should be actively monitored until values increase again.

Once all procedures and assessments for this visit are completed, an appointment for the next visit will be made and the subject will be discharged.

7.1.6 Month 6 Visit 3 (±7 days)

The following procedures and assessments will be performed at the Month 6 visit (Visit 3):

- A lymphocyte count as per mandatory monitoring at local laboratory facilities*
- Review of subject diary
- Treatment Satisfaction (TSQM v1.4)
- CCI [redacted]
- Assessment of AEs, concomitant medications and concomitant procedures

*Lymphocyte count will be checked locally after 6 months of starting treatment. If the lymphocyte count is below 500 cells/mm³, it should be actively monitored until values increase again.

Once all procedures and assessments for this visit are completed, an appointment for the next visit will be made and the subject will be discharged.

7.1.7 Month 12 Visit 4 (±7 days)

The following procedures and assessments will be performed at the Month 12 visit (Visit 4)***:

- Blood samples for serology and safety analysis at local laboratory (see Section 7.4.3)
- A lymphocyte count at local laboratory facilities *
- Review of subject diary
- Assessment of AEs, concomitant medications and concomitant procedures
- Physical examination including vital signs (blood pressure, heart rate, temperature)
- CCI [redacted]
- CCI [redacted]
- HRQoL
  - MSQoL-54
  - CCI [redacted]
  - CCI [redacted]

- Treatment Satisfaction (TSQM v1.4)
- CCI [redacted]
- Urine or Serum Pregnancy test (for female subjects of child-bearing potential only)
- Weight measurement and assignment of IMP via IRT
- Administration of trial medication and provision of trial medication intake for Month 13

*Lymphocyte count should be at least 800 cells/mm³ before initiating Mavenclad® in Year 2. If necessary, the treatment course in Year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes. If this recovery takes more than 6 months, the subject should not receive Mavenclad® anymore.

For patients with lymphocyte count below 800 cells/mm³, lymphocytes should be monitored and documented under unscheduled visits until the count is above 800 cells/mm³. Month 12 visit is split in this case into two parts (Month 12 with lymphocyte count, all efficacy parameters plus vital signs and physical examination. Month 12B - after recovery of lymphocytes - includes the safety parameters serology, TBC testing and pregnancy test plus weight and documentation of treatment administration). For patients with lymphocyte count above 800 cells/mm³ date of Month 12 and Month 12B is identical.

Once all procedures and assessments for this visit are completed, an appointment for the next visit will be made and the subject will be discharged.

**All assessments of Visit 4 will take place before the IMP administration

***An allowance window of 0-3 months will take place in case of delay in lymphocyte recovery to the levels mentioned in Section 5.4.1

7.1.8 Month 14 Visit 5 (±7 days)

Subjects will undergo**:

- A lymphocyte count as per mandatory monitoring, at local laboratory facilities *
- Review of subject diary
- Assessment of AEs, concomitant medications and concomitant procedures

*Lymphocyte count will be checked locally after 2 months of starting the 2nd course treatment. If the lymphocyte count is below 500 cells/mm³, it should be actively monitored until values increase again.

**An allowance window of 0-3 months will take place in case of delay in lymphocyte recovery to the levels mentioned in Section 5.4.1.

7.1.9 Month 18 Visit 6 (±7 days)

The following procedures and assessments will be performed at the Month 18 visit (Visit 6)**:

- A lymphocyte count as per mandatory monitoring, at local laboratory facilities *

- Review of subject diary
- CCI [redacted]
- Assessment of AEs, concomitant medications and concomitant procedures

*Lymphocyte count will be checked locally after 6 months of starting the 2nd course treatment. If the lymphocyte count is below 500 cells/mm³, it should be actively monitored until values increase again.

**An allowance window of 0-3 months will take place in case of delay in lymphocyte recovery to the levels mentioned in Section 5.4.1.

7.1.10 Final Visit/Early Termination/Month 24 Visit 7 (±7 days)

To complete the trial, the subject should return for a final evaluation at the end of Month 24**. In the event of early discontinuation from the trial, the subject should return for the Month 24 procedures outlined below. The reason for early discontinuation should be accurately assessed and entered into the eCRF.

The following procedures and assessments will be performed at the end of Month 24 visit:

- Lymphocyte count, at local laboratory facilities *
- Review of subject diary
- Physical examination including vital signs (including blood pressure, heart rate, temperature)
- MRI scan (see Section 7.3.5)
- CCI [redacted]
- CCI [redacted]
- HRQoL
  - MSQoL-54
  - CCI [redacted]
  - CCI [redacted]
- Treatment Satisfaction (TSQM v1.4)
- CCI [redacted]
- CCI [redacted]
- Assessment of AEs, concomitant medications and concomitant procedures

*Lymphocyte count should be at least 800 cells/mm³. If the lymphocyte count is below 500 cells/mm³, it should be actively monitored until values increase again.

**An allowance window of 0-3 months will take place in case of delay in lymphocyte recovery to the levels mentioned in Section 5.4.1.

7.1.11 Unscheduled Visits

A subject may return for an unscheduled visit at the discretion of the Investigator to undergo additional safety evaluations (i.e. laboratory retesting, AE assessments), or for neurological evaluations following a relapse. The data from unscheduled visits will be collected in the eCRF.

7.2 Demographic and Other Baseline Characteristics

At pre-Baseline visit, the following demographic data will be collected: date of birth, sex (gender), race, and ethnicity. Full details of the various assessments are detailed in the Schedule of Assessments in Section 7.1.

7.3 Efficacy Assessments

Neurological assessments CCI and CCI should be done by the Investigator. It is not needed to have separate rater for neurological assessments.

Responsible Site staff will be trained on MSQoL-54, CCI, TSQM v1.4, CCI before first test implementation to subject.

7.3.1 HRQoL

7.3.1.1 MSQoL-54

The MSQoL-54 questionnaire should be completed at Baseline and then at Months 12, and 24. The primary endpoint will be determined at Month 24 of this trial.

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. MSQoL-54 questionnaire (see Appendix 2: MSQoL-54 SCALE).

7.3.2 Treatment Satisfaction

7.3.2.1 TSQM v1.4

TSQM v1.4 questionnaire (see Appendix 8: TSQM v1.4 Questionnaire) should be completed at 6, 12 and 24 months to determine treatment satisfaction, which is a secondary endpoint in this trial. 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).

This questionnaire will be implemented in all countries where a local language translation from the author is available, and then included in study analysis where the questionnaire language is validated.

CCI


CCI

7.3.5 MRI

All scans will be performed according to a standard protocol detailed in a separate MRI scan user's manual.

7.3.5.1 Schedule

The MRI scans will be assessed at the Pre-Baseline Screening, and at Month 24.

7.3.5.2 MRI Scanning Procedure

The MRI measures of white matter lesional activity (i.e. new/enlarging T2 lesions or Gd-enhancing T1 lesions) and those of CCI) have shown to be valid surrogate endpoints for clinical outcomes.

The following MRI parameters will be measured for all subjects for each scan obtained during the trial:

- Active lesions defined as new T1 gadolinium-enhancing, or new T2 or enlarging T2 lesions (designated "CUL MRI lesions")
- T2 lesion volume
- CCI

All scans will be performed according to a standard protocol detailed in a separate Image Acquisition Guidelines (IAG) document. Investigator is responsible to ensure local radiologic analysis of the Screening MRI as per local standards of care to assess patient eligibility as well as to make further medical decisions related to this patient (see also Section 7.3.5.3.1). Central imaging core lab will independently perform the analysis of all MRI scans to meet study endpoints (see also

Section 7.3.5.3.2). As with other laboratory tests and clinical measures, strict adherence to the MRI scanning protocol, and prompt handling of the scans is essential in obtaining a meaningful result.

Investigator should also ensure that the MRI scan is locally evaluated for safety to rule out PML and/or any serious central nervous system disease (e.g., tumor, stroke etc). For patients switching from disease modifying treatments that have been previously linked to PML, the safety/eligibility assessment will be additionally assessed by central imaging core lab review (see also Section 7.3.5.3.3).

Prior to subject assessment, each trial site will be asked to send a 'test' or 'dummy-run' scan to assess image quality and shipment procedures, to evaluate the accessibility of the electronic data carrier, and to assess the ability to correctly reposition subjects so as to get comparable brain images. Only upon final approval of this test scan, sites will be allowed to begin assessing subjects.

Each subject should be scanned using the same machine throughout the trial. In case of machine change, or hardware/software upgrade the necessity to complete another test scan using the new equipment should be agreed with the central imaging core lab.

7.3.5.2.1 Data Handling

During the trial, the quality of each scan performed will be assessed by the central imaging core lab. As soon as the scan is received by the central imaging core lab, it will be evaluated for quality, completeness and adherence to the protocol. A case acceptance notification or query will be sent to the contributing site and the monitor. If scans are incomplete or incorrectly performed, the trial centre will be asked to repeat it as soon as possible.

After the quality check, all scans will be evaluated by the central imaging core lab that will analyze the variables. The electronic image data of the MRI scans will be stored at the central imaging core lab, and at the respective trial sites.

7.3.5.3 Evaluation of MRI Scans

7.3.5.3.1 Disease Diagnosis

All MRI scans will be locally obtained and assessed by the local neuroradiologist and or radiologist, following Standard of Care.

7.3.5.3.2 MRI Efficacy Endpoints

All collected MRI variables, for both Screening and Final visit MRI will be evaluated by the central reader. Results will not be shared with investigational sites.

For each scan, the MRI Investigator at each centre must send the electronic data for the images acquired without the corresponding plates to the central imaging core lab.

7.3.5.3.3 Evaluation of Screening MRI Scans for Eligibility

Investigator shall ensure safety evaluation of all MRIs by local radiologist/neuroradiologist

For subjects switching to Mavenclad® from any DMD potentially linked to PML as an adverse event should have their screening MRI sent to the central reader for verification of absence of PML. A non-exhaustive list of such DMDs includes:

- Natalizumab (Tysabri®)
- Fingolimod (Gilenya®)
- DMF (Tecfidera®)
- Alemtuzumab (Lemtrada®)
- Ocrelizumab (Ocrevus®)
- Mitoxantrone (Novantrone®)
- Rituximab (off label preparations) DMDs, previously

Screening MRI scans, accompanied by relevant clinical data available in EDC at the time of evaluation, from the above-mentioned subjects will be presented to the independent central reader, who will evaluate the MRI for signs of PML and provide the results of this evaluation to all relevant parties, as specified in the site operations manual and independent review committee documents.

CCI

CCI

[redacted]

7.4 Assessment of Safety

The safety profile of the IMP will be assessed through the recording, reporting and analysis of Baseline medical conditions, AEs, physical examination findings including vital signs and laboratory tests.

The incidence of TEAEs will be summarized by treatment group and overall, by severity, and by relationship to treatment. The summary tables will include incidence rates of TEAEs for overall system organ classes and by preferred term within each system organ class.

Comprehensive assessment of any apparent toxicity experienced by each subject will be performed from the time of giving informed consent and throughout the trial. The Investigator will report any AEs, whether observed by the Investigator or reported by the subject (see Section 7.4.1.2).

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product, regardless of causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

For surgical or diagnostic procedures, the condition/illness leading to such a procedure is considered as the AE rather than the procedure itself.

The Investigator is required to grade the severity or toxicity of each AE. Investigators must assess the severity of AEs according to the Qualitative Toxicity Scale, as follows:

- Mild: The subject is aware of the event or symptom, but the event or symptom is easily tolerated.
- Moderate: The subject experiences sufficient discomfort to interfere with or reduce his or her usual level of activity.
- Severe: Significant impairment of functioning: the subject is unable to carry out his or her usual activities.

Investigators must also systematically assess the causal relationship of AEs to IMPs (including any other non-IMPs, radiation therapy, etc.) using the following definitions. Decisive factors for the assessment of causal relationship of an AE to the IMPs include, but may not be limited to, temporal relationship between the AE and the IMPs, known side effects of IMPs, medical history, concomitant medication, course of the underlying disease, trial procedures.

Unrelated: Not reasonably related to the IMP. AE could not medically (pharmacologically/clinically) be attributed to the IMP under trial in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the IMP. AE could medically (pharmacologically/clinically) be attributed to the IMP under trial in this clinical trial protocol.

Abnormal Laboratory Findings and Other Abnormal Investigational Findings

Abnormal laboratory findings and other abnormal investigational findings (for example, on an electrocardiogram [ECG] trace) should not be reported as AEs unless they are associated with clinical signs and symptoms, lead to treatment discontinuation or are considered otherwise medically important by the Investigator. If a laboratory abnormality fulfills these criteria, the identified medical condition (for example, anemia, increased alanine aminotransferase [ALT]) must be reported as the AE rather than the abnormal value itself.

Serious Adverse Events

An SAE is any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening. (Note: The term "life-threatening" refers to an event in which the subject is at risk of death at the time of the event, not an event that hypothetically might have caused death if it was more severe.)
- Requires inpatient hospitalization or prolongs an existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is otherwise considered to be medically important. (Note: Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

For the purposes of reporting, any suspected transmission of an infectious agent via an IMP is also considered an SAE, as described in Section 7.4.1.4.

Events that Do Not Meet the Definition of an SAE

Elective hospitalizations to administer, or to simplify trial treatment or trial procedures (for example, an overnight stay to facilitate therapy) are not considered SAEs. However, all events leading to unplanned hospitalizations or unplanned prolongation of an elective hospitalization (for example, undesirable effects of any administered treatment) must be documented and reported as SAEs.

Events Not to Be Considered as AEs/SAEs

Medical conditions present at the initial trial visit that do not worsen in severity or frequency during the trial are defined as Baseline medical conditions, and are not to be considered AEs.

MS Relapses

In this protocol, symptoms and signs of relapse or worsening of MS will usually be captured in the context of the efficacy assessment, and recorded on the relapse module of the eCRF. Therefore, symptoms, relapses or worsening of MS will not be considered as AEs nor captured on the AE module of the eCRF unless considered possibly or probably related to the IMP (i.e. worsening is not consistent with the anticipated natural progression of the disease).

AE/SAEs Observed in Association with Disease Progression

Progression of the disease/disorder being studied assessed by measurement of lesions on radiographs or other methods as well as associated clinical signs or symptoms (including laboratory abnormalities) should not be reported as an (S)AE, unless the subjects's general condition is more severe than expected for the participant's condition and/or unless the outcome is fatal within the AE reporting period (as defined in Section 7.4.1.3).

Adverse Event of Special Interest

Not applicable.

7.4.1.2 Methods of Recording and Assessing Adverse Events

At each trial visit, the subject will be queried on changes in his or her condition. During the reporting period, any unfavorable changes in the subject's condition will be recorded as AEs, whether reported by the subject or observed by the Investigator.

Complete, accurate and consistent data on all AEs experienced for the duration of the reporting period (defined below) will be reported on an ongoing basis in the appropriate section of the CRF. All SAEs must be additionally documented and reported in the SAE eCRF page as described in Section 7.4.1.4.

It is important that each AE report include a description of the event, its duration (onset and resolution dates and times when it is important to assess the time of AE onset relative to the recorded treatment administration time), its severity, its causal relationship with the trial treatment, any other potential causal factors, any treatment given or other action taken, including dose modification or discontinuation of the IMP, and its outcome. In addition, serious cases should be identified and the appropriate seriousness criteria documented.

Specific guidance can be found in the CRF Completion and Monitoring Conventions provided by the Sponsor.

7.4.1.3 Definition of the Adverse Event Reporting Period

The AE reporting period for safety surveillance begins when the subject is initially included in the trial (date of first signature of informed consent/date of first signature of first informed consent) and continues until at end of month 24 as per the Final Visit guidelines.

Any SAE assessed as related to Mavenclad® must be reported whenever it occurs, irrespective of the time elapsed since the last administration of Mavenclad®.

7.4.1.4 Procedure for Reporting Serious Adverse Events

Serious Adverse Events

In the event of any new SAE occurring during the reporting period, the Investigator must immediately (within a maximum of 24 HOURS after becoming aware of the event) inform the Sponsor or its designee in the eCRF SAE page, which must be completed by the Investigator following specific completion instructions.

In case the eCRF is not available, the SAEs must be reported via email using the paper SAE Report Form following specific completion instructions. Also in exceptional circumstances, an SAE (or follow-up information) may be reported by telephone; in these cases the CRF must be completed as soon as it becomes available.

Relevant pages from the CRF may be provided in parallel (for example, medical history, concomitant drugs). Additional documents may be provided by the Investigator, if available (for example, laboratory results, hospital report, autopsy report). In all cases, the information provided on the SAE Report Form must be consistent with the data about the event recorded in the CRF.

The Investigator must respond to any request for follow-up information (for example, additional information, outcome, final evaluation, other records where needed) or to any question the Sponsor/designee may have on the AE within the same timelines as those noted above for initial reports. This is necessary to ensure prompt assessment of the event by the Sponsor or designee and (as applicable) to allow the Sponsor to meet strict regulatory timelines associated with expedited safety reporting obligations.

Requests for follow-up will usually be made via the responsible Monitor, although in exceptional circumstances the Global Drug Safety department may contact the Investigator directly to obtain further information or to discuss the event.

7.4.1.5 Safety Reporting to Health Authorities, Independent Ethics Committees/ Institutional Review Boards and Investigators

The Sponsor will send appropriate safety notifications to Health Authorities in accordance with applicable laws and regulations. The Investigator must comply with any applicable site-specific requirements related to the reporting of SAEs (particularly deaths) involving trial subjects to the IEC/IRB that approved the trial.

In accordance with ICH GCP, the Sponsor/designee will inform the Investigator of "findings that could adversely affect the safety of subjects, impact the conduct of the trial or alter the IEC's/IRB's approval/favorable opinion to continue the trial." In particular and in line with respective regulations, the Sponsor/designee will inform the Investigator of AEs that are both serious and unexpected and are considered to be related to the administered product ("suspected unexpected serious adverse reactions" or suspected unexpected serious adverse reaction [SUSARs]). The Investigator should

place copies of Safety Reports in the Investigator Site File. National regulations with regard to Safety Report notifications to Investigators will be taken into account.

When specifically required by regulations and guidelines, the Sponsor/designee will provide appropriate Safety Reports directly to the concerned lead IEC/IRB and will maintain records of these notifications. When direct reporting is not clearly defined by national or site-specific regulations, the Investigator will be responsible for promptly notifying the concerned IEC/IRB of any Safety Reports provided by the Sponsor/designee and of filing copies of all related correspondence in the Investigator Site File.

For trials covered by the European Directive 2001/20/EC, the Sponsor's responsibilities regarding the reporting of SAEs/SUSARs/Safety Issues will be carried out in accordance with that Directive and with the related Detailed Guidance documents.

7.4.1.6 Monitoring of Subjects with Adverse Events

AEs are recorded and assessed continuously throughout the trial and are assessed for final outcome at the End of Trial visit. All SAEs ongoing at the End of Trial visit must be monitored and followed up by the Investigator until stabilization or until the outcome is known, unless the subject is documented as "lost to follow-up". Reasonable attempts to obtain this information must be made and documented. It is also the responsibility of the Investigator to ensure that any necessary additional therapeutic measures and follow-up procedures are performed.

Monitoring of Specific Adverse Events

Not applicable.

7.4.2 Pregnancy and In Utero Drug Exposure

Only pregnancies considered by the Investigator to be related to trial treatment (for example, resulting from a drug interaction with a contraceptive medication) are considered to be AEs. However, all pregnancies with an estimated conception date during the period defined in Section 7.4.1.3 must be recorded by convention in the AE page/section of the CRF. The same rule applies to pregnancies in female subjects and to pregnancies in female partners of male subjects. The Investigator must notify the Sponsor/designee in an expedited manner of any pregnancy using the Pregnancy Report Form, which must be transmitted via an email immediately (within a maximum of 24 hours after becoming aware of the event), following specific completion instructions.

Investigators must actively follow up, document and report on the outcome of all these pregnancies, even if the subjects are withdrawn from the trial.

The Investigator must notify the Sponsor/designee of these outcomes using the Pregnancy Report Form. If an abnormal outcome occurs, the SAE Report Form will be used if the subject sustains an event and the Parent-Child/Fetus AE Report Form if the child/fetus sustains an event.

Any abnormal outcome must be reported in an expedited manner as described in Section 7.4.1.4, while normal outcomes must be reported within 45 days after delivery.

In the event of a pregnancy in a subject occurring during the course of the trial, the subject must be discontinued from trial medication immediately. The Sponsor/designee must be notified without delay and the subject must be followed as mentioned above.

7.4.3 Clinical Laboratory Assessments

Local clinical laboratory samples will be collected for screening, post-treatment effect (Months 2, 6, 14, 18) and emergency safety evaluations but are not required to be collected/recorded in the CRFs (see Table 3).

Table 3: Local laboratory assessments

Screening	Hematology	Lymphocyte count
	Serology	Hepatitis B, Hepatitis C, HIV, VZV**
	TB screening as per local standard of care*	TB (active and/or latent)
	MRI	Following established protocol of MRI sequences, described in IAG
	Urine and/or serum tests	Pregnancy
Baseline	Hematology	Lymphocyte count to be repeated if interval is more than 4 weeks from screening sample
	Urine and/or serum tests	Pregnancy
Post-treatment (Year 1 and 2)	Hematology	Lymphocyte count at 2, 6, 12, 14, 18, 24 months
Before Year 2 dosing	Hematology	Lymphocyte count
	Urine and/or serum tests	Pregnancy
	Serology	Hepatitis B, Hepatitis C, HIV
	TB screening as per local standard of care*	TB (active and/or latent)

Abbreviations: CT=computerised tomography; HIV=human immunodeficiency virus; IAG = image acquisition manual; MRI=magnetic resonance imaging; MS=multiple sclerosis; PML=progressive multifocal leukoencephalopathy; TB=Tuberculosis; VZV=varicella zoster virus.

* Imaging (e.g., chest X-ray, chest CT scan, MRI) and/or positive QuantiFERON-TB Gold test and/or skin test and/or clinical examination

** Only if the patient has no history of varicella infection or immunity

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital signs including body temperature, respiratory rate, and heart rate (after 5-minute rest) and arterial blood pressure (after 5-minute rest) will be measured once at Screening and at visits 4 (month 12) and 7 (month 24).

A complete physical examination (including, e.g., general appearance, skin, head/neck, pulmonary, cardiovascular, gastrointestinal, external genitourinary, lymphatic, musculoskeletal system,

extremities, eyes [inspection and vision control], nose, throat, and neurologic status) will be performed at screening and at subsequent visits as documented in the Schedule of Assessments (Appendix 1: Schedule of Assessments) and the abnormal results documented in the CRF. All clinically significant abnormalities occurring before signature of informed consent should be recorded in the Medical History section and/or Disease History; all abnormalities occurring or worsening after signature of informed consent should be recorded in the AEs section. Abnormal findings are to be reassessed at subsequent visits.

Body weight will be recorded at Baseline and at month 12, before the treatment administration, as indicated in the Schedule of Assessments (Appendix 1: Schedule of Assessments) and documented in the CRF. All newly diagnosed conditions, signs, and symptoms observed from screening, whether related to trial medication or not, are to be reported as AEs. The relapse will not be reported as an AE and will be captured in a dedicated eCRF page for efficacy analysis.

7.5 Pharmacokinetics

Not applicable.

7.6 Biomarkers

Not applicable.

7.7 Other Assessments

Not applicable

8 Statistics

CCI

CCI

8.2 Randomization

Not applicable

8.3 Endpoints

8.3.1 Primary Endpoint(s)

- Changes in MSQoL-54 at 24 months compared to Baseline, i.e. the changes in the physical and mental health composite scores

8.3.2 Secondary Endpoint

- Treatment global satisfaction assessed by TSQM v1.4 at 6 months

8.4 Analysis Sets

Enrolled Set: All subjects enrolled.

Intent-to-treat Set (ITT): All subjects classified as eligible.

Full Analysis Set (FAS): All subjects from the ITT treated with at least one dose of trial treatment.

Treatment Completer Set – Year 1: All subjects from the FAS who completed the full treatment course of the first year.

Treatment Completer Set – Year 2: All subjects from the FAS who completed the full treatment course of the first and the second year.

Safety Set: All subjects treated with at least one dose of trial treatment.

The primary analyses and all efficacy analyses will be performed on the FAS. The primary and secondary analyses will be repeated for the Treatment Completer Sets and the primary for the ITT, if different. All safety analyses will be performed on the Safety Set.

Subjects who have withdrawn consent for the trial will be included in the analysis unless it was specified by them that their data not be used, after clarification of the level of withdrawal by the Investigator.

8.5 Description of Statistical Analyses

The statistical analyses described in this section will be performed as further outlined in the SAP, which will be finalized prior to database lock and will be included in the clinical trial report for this protocol. The final SAP will take into account any amendment to the protocol

8.5.1 General Considerations

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.

For analysis of all endpoints, differences with a p-value of 0.05 or less will be considered nominally statistically significant. Parameter estimates with associated 95% confidence intervals will be reported in each analysis.

Subjects' demographic factors and Baseline clinical characteristics will be summarized with the following measures: mean with standard deviation, minimum and maximum for normally distributed continuous variables, median with interquartile range, minimum and maximum for other continuous variables and counts with percentages for categorical variables.

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-centre trial, it is likely that clustering of individuals within trial sites will produce an additional source of correlation. Mixed-effects regression, whereby a three-level hierarchical model is specified for

observations within subjects within trial sites, will be used to account for within-subject and within-centre correlation (Gibbons et al., 2010).

Assessment schedules

It is likely that the 2nd year treatment may be delayed substantially for a small number of subjects for whom the second dose is not required immediately. Due to the need for a finite follow-up period, a buffer of 3 months is given for subjects who do not receive the second treatment at the specified time. 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.

In each analysis, should assessment be delayed, subjects' assessment data will be treated as though it occurred at the time point specified and inferences will be conducted accordingly.

Missing data

Should missing data be present in Baseline covariates included in the analysis models, mean or median imputation and use of a missing indicator will be used for continuous and categorical covariates, respectively.

The trial dataset comprises of multiple outcome assessments made for each subject over a 24-month period. Therefore, due to the longitudinal nature of the data and the lengthy follow-up period, it is likely that missing outcome data will be present due to loss to follow-up. Patterns and degrees of missingness will be summarized and will inform the approach taken to dealing with missing data.

8.5.2 Analysis of Primary Endpoints

The primary endpoints for the trial 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 24 months and Baseline will be assessed using mixed-effects linear regression, accounting for within-subject correlation and within-centre/region correlation (see Section 8.5.1 for details). The analysis will also adjust for factors deemed to be prognostic for the primary endpoint, as judged by clinical experts.

Linear regression modelling assumes that outcomes are normally distributed. Appropriate transformations (such as square root or log transform) may be used to achieve normality.

An estimate for the mean difference in MSQol-24 scores between Baseline and 24 months will be reported, with a 95% confidence interval and two-sided p-value. The interim analysis at 6 months will be considered as supportive of the 24-months analysis (main analysis), and thus, does not require adjustment for multiplicity.

8.5.3 Analysis of Secondary and CCI [redacted]

Analysis comparing continuous secondary and CCI [redacted] (including scores) measured repeatedly at specific time points will be undertaken using similar techniques to those outlined for the primary analysis. Models will be adjusted to include Baseline as available. If only one

measurement is available (e.g., for 6 months) the models will be simplified as the within-subject correlation cannot be estimated.

[redacted]

Other outcomes (e.g., subscores and scales) will be summarized descriptively.

To assess correlation between the HRQoL assessed by MSQoL-54 and [redacted], appropriate statistics such as the Pearson product-moment correlation coefficient and R^2 statistic will be produced alongside visual summaries.

Information on TEAEs and SAEs these events will be collected and summarized accordingly, providing detail of the frequency, type, severity and outcome of the events.

8.6 Interim and Additional Planned Analyses

An interim analysis will be undertaken after all subjects have completed the 6-month assessment. This will include analysis of the outcome TSQM v1.4, including all assessment data up to and including the 6-month assessment. A descriptive analysis will also be undertaken, including summaries of Baseline characteristics, outcome measures and adverse events. For efficacy endpoints, the analysis at 6 months will be considered as supportive of the 24-month analysis (main analysis).

9 Ethical and Regulatory Aspects

9.1 Responsibilities of the Investigator

The Investigator is responsible for the conduct of the trial at the site and will ensure that the trial is performed in accordance with this protocol, the ethical principles outlined in the Declaration of Helsinki, ICH GCP and any other applicable regulations. The Investigator must ensure that only subjects who have given informed consent are included in the trial.

9.2 Subject Information and Informed Consent

An unconditional prerequisite for each subject prior to participation in the trial is written informed consent, which must be given before any trial-related activities are carried out. Adequate information must therefore be given to the subject by the Investigator or an appropriate designee (if local regulations permit) before informed consent is obtained.

A subject information sheet must be prepared in the local language in accordance with ICH GCP and will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or a designee will inform the subject verbally of all pertinent aspects of the trial, using language chosen so that the information can be fully and readily understood by laypersons. The subject will be given sufficient time to read

the information and the opportunity to ask questions and to request additional information and clarification.

If permitted by national regulations, a person other than the Investigator may inform the subject about the trial and sign the ICF, as above.

After the information is provided by the Investigator, the ICF must be signed and dated by the subject and the Investigator.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived so that the forms can be retrieved at any time for monitoring, auditing and inspection purposes. The process of Informed Consent collection must be clearly documented in the source notes. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Whenever important new information becomes available that may be relevant to informed consent, the Sponsor will revise the subject information sheet and any other written information to be provided to the subjects and Investigator will submit them to the IRB/IEC for review and opinion. Using the approved revised subject information sheet and other written information, the Investigator will explain the changes to the previous version to each trial subject and obtain new written consent for continued participation in the trial. The subject will be given sufficient time to read the information and the opportunity to ask questions and to request additional information and clarification about the changes.

9.3 Subject Identification and Privacy

A unique number will be assigned to each subject, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. All subject data collected in the trial will be stored under the appropriate subject number. Only the Investigator will be able to link trial data to an individual subject via an identification list kept at the site. For each subject, original medical data will be accessible for the purposes of source data verification by the Monitor, audits and regulatory inspections, but subject confidentiality will be strictly maintained.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly, and will be requested to give their consent on data handling procedures in accordance with national regulations.

9.4 Emergency Medical Support and Subject Card

Subjects will be provided with Emergency Medical Support cards supplied by the Sponsor for use during trial participation in order to provide clinical trial subjects with a way of identifying themselves as participating in a clinical trial and to give health care providers access to any information about this participation that may be needed to determine the course of medical treatment for the subject.

The first point of contact for all emergencies will be the clinical trial Investigator caring for the affected subject. The Investigator agrees to provide his or her emergency contact information on the

card for this purpose. If the Investigator is available when an event occurs, they will answer any questions. Any subsequent action will follow the standard process established for Investigators.

9.5 Clinical Trial Insurance and Compensation to Subjects

Insurance coverage will be provided for each country participating to the trial. Insurance conditions shall meet good local standards, as applicable.

9.6 Independent Ethics Committee or Institutional Review Board

Prior to commencement of the trial at a given site, this clinical trial protocol will be submitted together with its associated documents to the responsible IEC or IRB for its favorable opinion or approval, which will be filed in the Investigator Site File. A copy will be filed in the Sponsor Trial Master File.

The IEC or IRB will be asked to document the date of the meeting at which the favorable opinion or approval was given and the members and voting members present. Written evidence of favorable opinion or approval that clearly identifies the trial, the clinical trial protocol version and the Subject Information and ICF version reviewed should be provided. Where possible, copies of the meeting minutes should be obtained.

Amendments to this clinical trial protocol will also be submitted to the concerned IEC or IRB, before implementation of substantial changes (see Section 10.5). Relevant safety information will be submitted to the IEC or IRB during the course of the trial in accordance with national regulations and requirements.

9.7 Health Authorities

The clinical trial protocol and any applicable documentation (for example, Investigational Medicinal Product Dossier, Subject Information and ICF) will be submitted or notified to the Health Authorities in accordance with all local and national regulations for each site.

10 Trial Management

10.1 Case Report Form Handling

Refer to the eCRF Completion Instructions.

The main purpose of the eCRF is to obtain data required by the clinical trial protocol in a complete, accurate, legible and timely. The data in the eCRF should be consistent with the relevant source documents.

The Investigator or designee is responsible for ensuring that the data collected in the course of this trial is accurate and documented appropriately on all applicable forms. They will then be processed, evaluated, and stored in anonymous form in accordance with applicable data protection regulations. The Investigator must ensure that the eCRFs and any other associated documents forwarded to Sponsor or its designated organization contain no mention of any subject names.

For patient-reported outcome data such as QoL, ePRO will be used.

The data will be entered into a validated database. The Sponsor or its designee will be responsible for data processing, in accordance with the Sponsor's data management procedures. Database lock will occur once quality control and quality assurance procedures have been completed. PDF files of the eCRFs will be provided to the Investigators at the completion of the trial.

10.2 Source Data and Subject Files

The Investigator must keep a file (medical file, original medical records) on paper or electronically for every subject in the trial. It must be possible to identify each subject by using this subject file. This file will contain the demographic and medical information for the subject listed below and should be as complete as possible.

- Subject's full name, date of birth, sex, height, weight
- Medical history and concomitant diseases
- Prior and concomitant therapies (including changes during the trial)
- Trial identification, that is, the Sponsor trial number for this clinical trial, and subject number
- Dates for entry into the trial (informed consent) and visits to the site
- Any medical examinations and clinical findings predefined in this clinical trial protocol
- All AEs
- Date that the subject left the trial including any reason for early withdrawal from the trial or IMP (if applicable).

All documents containing source data must be filed, including, but not limited to CT or MRI scan images, and laboratory results. Such documents must bear the subject number and the date of the procedure. If possible, this information should be printed by the instrument used to perform the assessment or measurement. As necessary, medical evaluation of such records should be performed; all evaluations should be documented, signed, and dated by the Investigator.

Electronic subject files will be printed whenever the Clinical research associate performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the CRA and kept in a safe place at the site.

10.3 Investigator Site File and Archiving

Upon initiation of the trial, the Investigator will be provided with an Investigator Site File containing all necessary trial documents, which will be completed throughout the trial and updated as necessary. The file must be available for review by the Monitor, during Sponsor audits and for inspection by Health Authorities during and after the trial, and must be safely archived for at least 15 years (or longer, per local requirements or as otherwise notified by the Sponsor) after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor/designee.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and/or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

10.4 Monitoring, Quality Assurance and Inspection by Health Authorities

This trial will be monitored in accordance with the ICH GCP, and any other applicable regulations. The site Monitor will perform visits to the trial site at regular intervals.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent Quality Assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data. Representatives of the Quality Assurance unit from the Sponsor or a designated organization, as well as Health Authorities, must be permitted to access all trial documents and other materials at the site, including the Investigator Site File, the completed CRFs, all IMP and IMP accountability records, and the original medical records or files for each subject.

10.5 Changes to the Clinical Trial Protocol

Changes to the clinical trial protocol will be documented in writing. Substantive amendments will usually require submission to the Health Authorities and to the relevant IEC/IRB for approval or favorable opinion. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

Minor (non-substantial) protocol amendments, including administrative changes, will be filed by the Sponsor and at the site. They will be submitted to the relevant IEC/IRB or to Health Authorities only where requested by pertinent regulations. Any amendment that could affect the subject's agreement to participate in the trial requires additional informed consent prior to implementation following the process as described in Section 9.2.

10.6 Clinical Trial Report and Publication Policy

10.6.1 Clinical Trial Report

After completion of the trial, a clinical trial report will be written by the Sponsor in consultation with the Coordinating Investigator following the guidance in ICH Topic E3.

10.6.2 Publication

The first publication will include the results of the analysis of the primary endpoints and will include data from all trial sites. The Investigator will inform the Sponsor in advance about any plans to publish or present data from the trial. Any publications and presentations of the results (abstracts in journals or newspapers, oral presentations, etc.), either in whole or in part, by Investigators or their representatives will require review by the Sponsor before submission. The Sponsor will not suppress publication, but maintains the right to delay publication in order to protect intellectual property rights.

Posting of data on the European Clinical Trials Register and ClinicalTrials.gov is planned and will occur 12 months after the last clinic visit of the final trial subject or another appropriate date to meet applicable requirements.

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12 Appendices

12.1 Appendix 1: Schedule of Assessments

Visit		1	2	3	4	5	6	7
Time of Assessments*	Screening**	Baseline	Month 2 (±7 days)	Month 6 (±7 days)	Month 12 (±7 days)[a]	Month 14 (±7 days)[a]	Month 18 (±7 days)[a]	Month 24 (±7 days)[a]
Informed Consent[b]	X							
IRT[c]		X			X			
Weight		X			X			
Vital Signs	X				X			X
Physical Examination	X				X			X
Medical History	X							
Disease History	X							
CCI								
Lymphocyte Count[e]	X	X	X	X	X	X	X	X
HRQoL (MSQoL-54)		X			X			X
Treatment Satisfaction (TSQM v1.4)				X	X			X
CCI								
MRI	X							X
Serology (HIV, HBV, HCV, VZV)	X[h]				X[f]			
TB Screening	X				X			

Pregnancy test[g]	X	X			X			
Subject Diary		X	X	X	X	X	X	X
AEs		X	X	X	X	X	X	X

[a] An allowance window of 0-3 months will take place in case of delay in lymphocyte recovery to the levels mentioned in Section 5.4.1.
[b] The ICF should be signed by the subject before any changes in the concomitant medications are made.
[c] Interactive Response Technology for assignment of subject ID number and IMP accountability.
[d] Trial visits for subjects who are relapsing will be required to perform the outcome evaluation at the resolution of the relapse, when it is appropriate for the subject to complete trial visit assessments.
[e] Lymphocyte count should be (i) normal before initiating cladribine in year 1, (ii) at least 800 cells/mm³ before initiating in year 2 (iii) checked at 2 and 6 months after start of treatment in each treatment year. If necessary, the treatment course in year 2 can be delayed for up to 6 months to allow for recovery of lymphocytes. If this recovery takes more than 6 months, cladribine treatment should be terminated.
[f] Only for HIV, HBV and HCV.
[g] Urine or serum test will be done according to local regulations.
[h]: If the local laboratory blood test for serology and safety analysis is conducted within 10 days of the Screening visit, no blood samples need to be repeated.
[*] The order of assessments will be MSQoL-54, TSQM v1.4, CCI [redacted]
[**] In certain cases, screening period may be longer than 4 weeks (see Section 7.1.1)
[***] If the neurological examination at the Screening visit is conducted within 10 days of Baseline and the subject reports no change in status, no neurological examination needs to be repeated on Baseline (Visit 1).

12.2 Appendix 2: MSQoL-54 SCALE

Multiple Sclerosis Quality of Life (MSQoL)-54 Instrument

INSTRUCTIONS:
This survey asks about your health and daily activities. Answer every question by selecting the appropriate number (1, 2, 3...).
If you are unsure about how to answer a question, please give the best answer you can.
Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is:

(select one number)

Excellent.....1

Very good.....2

Good.....3

Fair.....4

Poor.....5

2. **Compared to one year ago**, how would you rate your health in general **now**?

(select one number)

Much better now than one year ago.....1

Somewhat better now than one year ago.....2

About the same as one year ago.....3

Somewhat worse now than one year ago.....4

Much worse now than one year ago.....5

3-12. The following questions are about activities you might do during a typical day. Does **your health** now limit you in these activities? If so, how much?
(Select 1, 2, or 3 on each line)

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
4. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
5. Lifting or carrying groceries	1	2	3
6. Climbing several flights of stairs	1	2	3
7. Climbing one flight of stairs	1	2	3
8. Bending, kneeling, or stooping	1	2	3
9. Walking more than a mile	1	2	3
10. Walking several hundred yards	1	2	3
11. Walking one hundred yards	1	2	3
12. Bathing and dressing yourself	1	2	3

13-16. During the **past 4 weeks** have you had any of the following problems with your work or other regular daily activities **as a result of your physical health?**
(Select one number on each line)

	YES	NO
13. Cut down on the amount of time you spent on work or other activities	1	2
14. Accomplished less than you would like	1	2
15. Were limited in the kind of work or other activities	1	2
16. Had difficulty performing the work or other activities (for example, it took extra effort)	1	2

17-19. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?
(Select one number on each line)

	YES	NO
17. Cut down on the amount of time you spent on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Did work or other activities less carefully than usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

(select one number)

Not at all.....1

Slightly.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

Pain

21. How much **bodily** pain have you had during the **past 4 weeks**?

(select one number)

None.....1

Very mild..... 2

Mild..... 3

Moderate..... 4

Severe.....5

Very severe..... 6

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

(select one number)

Not at all.....1

A little bit.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

23-32. These questions are about how you feel and how things have been for you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

(Select one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of life?	1	2	3	4	5	6
24. Have you been very nervous?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and low?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been happy?	1	2	3	4	5	6

31. Did you feel tired?	1	2	3	4	5	6
32. Did you feel rested on waking in the morning?	1	2	3	4	5	6

33. During the **past 4 weeks**, how much of the time has your **physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?
(select one number)

All of the time.....1

Most of the time.....2

Some of the time.....3

A little of the time.....4

None of the time.....5

Health in General

34-37. How TRUE or FALSE is each of the following statements for you?
(Select one number on each line)

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
34. I seem to get ill more easily than other people	1	2	3	4	5
35. I am as healthy as anybody I know	1	2	3	4	5
36. I expect my health to get worse	1	2	3	4	5
37. My health is excellent	1	2	3	4	5

Health Distress

How much of the time during the **past 4 weeks**...

(Select one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
38. Were you discouraged by your health problems?	1	2	3	4	5	6
39. Were you frustrated about your health?	1	2	3	4	5	6
40. Was your health a worry in your life?	1	2	3	4	5	6
41. Did you feel weighed down by your health problems?	1	2	3	4	5	6

Cognitive Function

How much of the time during the **past 4 weeks**...

(Select one number on each line)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
42. Have you had difficulty concentrating and thinking?	1	2	3	4	5	6
43. Did you have trouble keeping your attention on an activity for long?	1	2	3	4	5	6
44. Have you had trouble with your memory?	1	2	3	4	5	6
45. Have others, such as family members or friends, noticed that you have trouble with your memory or problems with your concentration?	1	2	3	4	5	6

Sexual Function

46-50. The next set of questions are about your sexual function and your satisfaction with your sexual function. Please answer as accurately as possible about your function **during the past 4 weeks only.**

How much of a problem was each of the following for you **during the past 4 weeks?**

(Select one number on each line)

MEN	Not a problem	A little of a problem	Somewhat of a problem	Very much a problem	Not applicable
46. Lack of sexual interest	1	2	3	4	5
47. Difficulty getting or keeping an erection	1	2	3	4	5
48. Difficulty having an orgasm	1	2	3	4	5
49. Ability to satisfy sexual partner	1	2	3	4	5

(Select one number on each line)

WOMEN	Not a problem	A little of a problem	Somewhat of a problem	Very much a problem	Not applicable
46. Lack of sexual interest	1	2	3	4	5
47. Inadequate lubrication	1	2	3	4	5
48. Difficulty having an orgasm	1	2	3	4	5
49. Ability to satisfy sexual partner	1	2	3	4	5

50. Overall, how satisfied were you with your sexual function **during the past 4 weeks**?

(select one number)

Very satisfied..... 1

Somewhat satisfied..... 2

Neither satisfied nor dissatisfied.....3

Somewhat dissatisfied.....4

Very dissatisfied.....5

51. During the **past 4 weeks**, to what extent have problems with your bowel or bladder function interfered with your normal social activities with family, friends, neighbours, or groups?

(select one number)

Not at all..... 1

Slightly.....2

Moderately.....3

Quite a bit.....4

Extremely.....5

52. During the **past 4 weeks**, how much did *pain* interfere with your enjoyment of life?

(select one number)

Not at all.....1

Slightly.....2

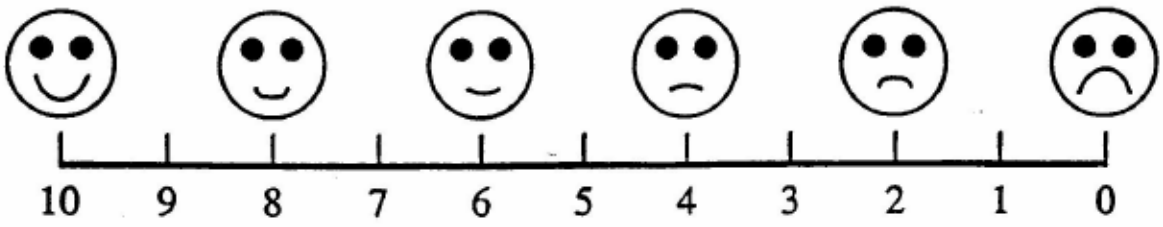
Moderately.....3

Quite a bit.....4

Extremely..... 5

54. Overall, how would you rate your own quality of life?

Select one number on the scale below:



Best possible quality of life

Worst possible quality of life
As bad as or worse than being dead

54. Which best describes how you feel about your life as a whole?

(select one number)

Terrible.....1

Unhappy.....2

Mostly dissatisfied.....3

Mixed - about equally satisfied and dissatisfied.....4

Mostly satisfied.....5

Pleased.....6

Delighted.....7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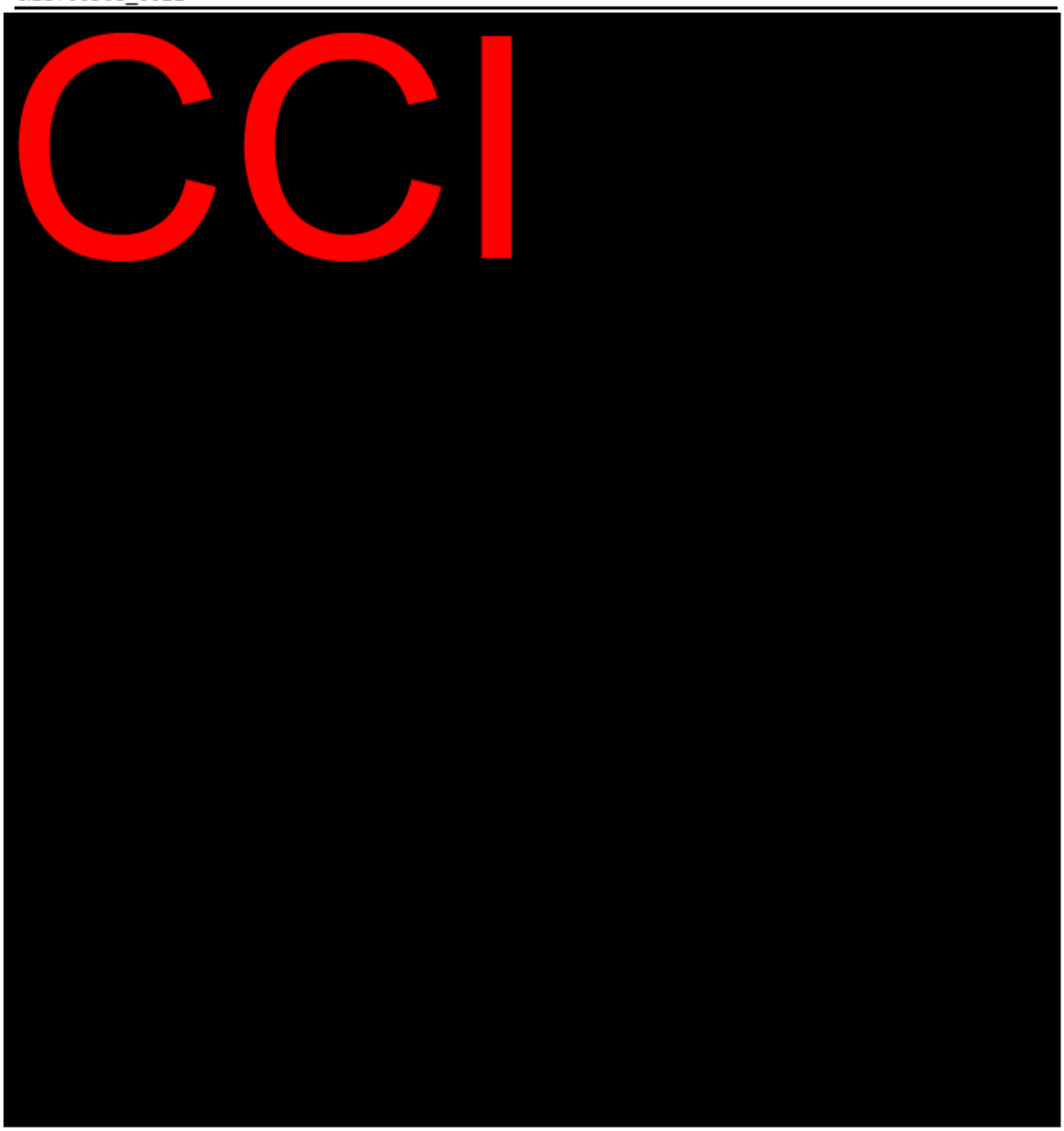
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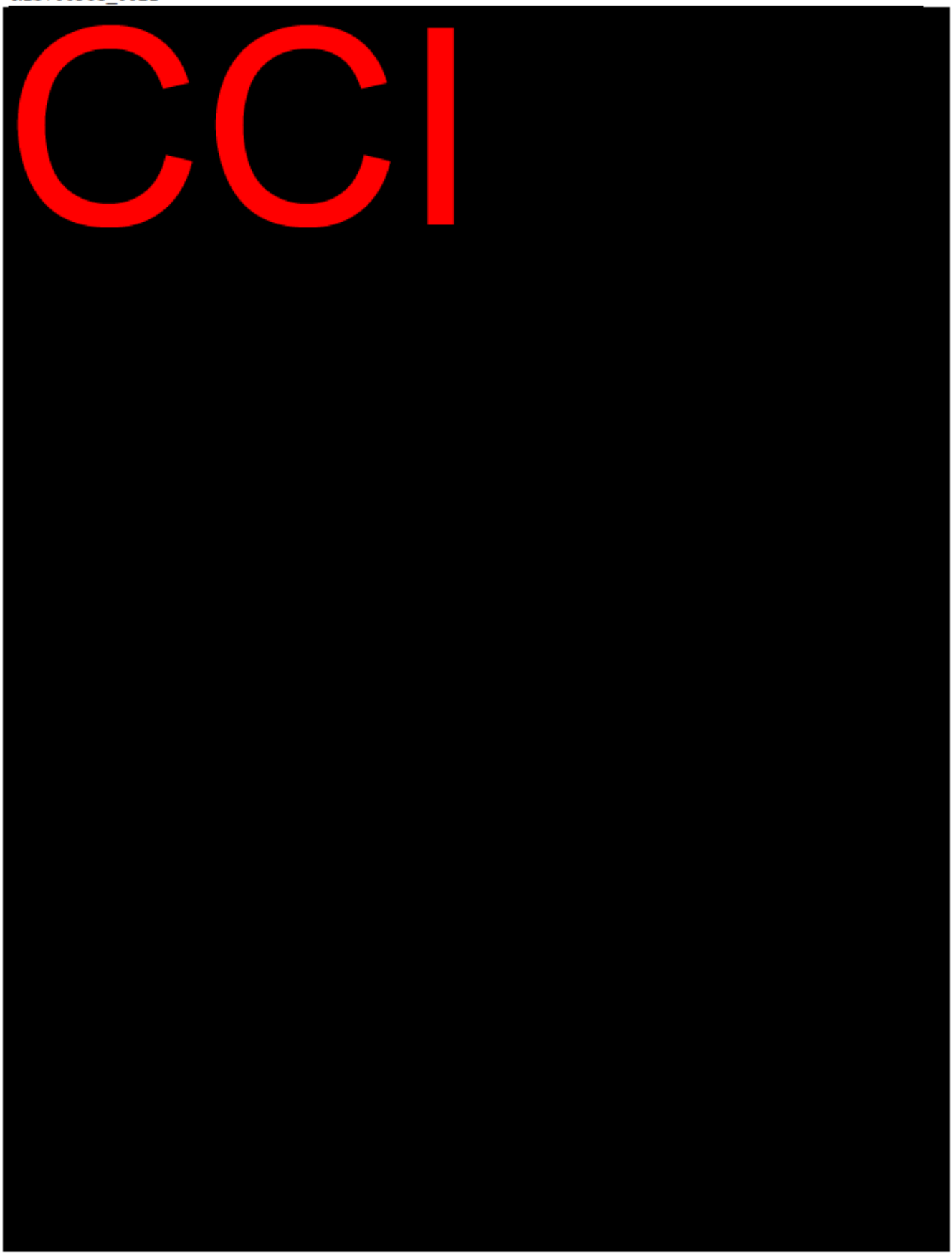
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12.8 Appendix 8: TSQM v1.4 Questionnaire

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat your condition?

☐ Extremely Dissatisfied

☐ Very Dissatisfied

☐ Dissatisfied

☐ Somewhat Satisfied

☐ Satisfied

☐ Very Satisfied

☐ Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves your symptoms?

☐ Extremely Dissatisfied

☐ Very Dissatisfied

☐ Dissatisfied

☐ Somewhat Satisfied

☐ Satisfied

☐ Very Satisfied

☐ Extremely Satisfied

3. How satisfied or dissatisfied are you with the amount of time it takes the medication to start working?

☐ Extremely Dissatisfied

☐ Very Dissatisfied

☐ Dissatisfied

☐ Somewhat Satisfied

☐ Satisfied

☐ Very Satisfied

☐ Extremely Satisfied

4. As a result of taking this medication, do you experience any side effects at all?

☐ Yes

☐ No (if No, then please skip to Question 9)

5. How bothersome are the side effects of the medication you take to treat your condition?

☐ Extremely Bothersome

☐ Very Bothersome

☐ Somewhat Bothersome

☐ A Little Bothersome

☐ Not at All Bothersome

6. To what extent do the side effects interfere with your physical health and ability to function (i.e., strength, energy levels, etc.)?

☐ A Great Deal

☐ Quite a Bit

☐ Somewhat

☐ Minimally

☐ Not at All

7. To what extent do the side effects interfere with your mental function (i.e., ability to think clearly, stay awake, etc.)?

☐ A Great Deal

☐ Quite a Bit

☐ Somewhat

☐ Minimally

☐ Not at All

8. To what degree have medication side effects affected your overall satisfaction with the medication?

☐ A Great Deal

☐ Quite a Bit

☐ Somewhat

☐ Minimally

☐ Not at All

9. How easy or difficult is it to use the medication in its current form?

☐ Extremely Difficult

☐ Very Difficult

☐ Difficult

☐ Somewhat Easy

☐ Easy

☐ Very Easy

☐ Extremely Easy

10. How easy or difficult is it to plan when you will use the medication each time?

☐ Extremely Difficult

☐ Very Difficult

☐ Difficult

☐ Somewhat Easy

☐ Easy

☐ Very Easy

☐ Extremely Easy

11. How convenient or inconvenient is it to take the medication as instructed?

☐ Extremely Inconvenient

☐ Very Inconvenient

☐ Inconvenient

☐ Somewhat Convenient

☐ Convenient

☐ Very Convenient

☐ Extremely Convenient

12. Overall, how confident are you that taking this medication is a good thing for you?

☐ Not at All Confident

☐ A Little Confident

☐ Somewhat Confident

☐ Very Confident

☐ Extremely Confident

13. How certain are you that the good things about your medication outweigh the bad things?

☐ Not at All Certain

☐ A Little Certain

☐ Somewhat Certain

☐ Very Certain

☐ Extremely Certain

14. Taking all things into account, how satisfied or dissatisfied are you with this medication?

☐ Extremely Dissatisfied

☐ Very Dissatisfied

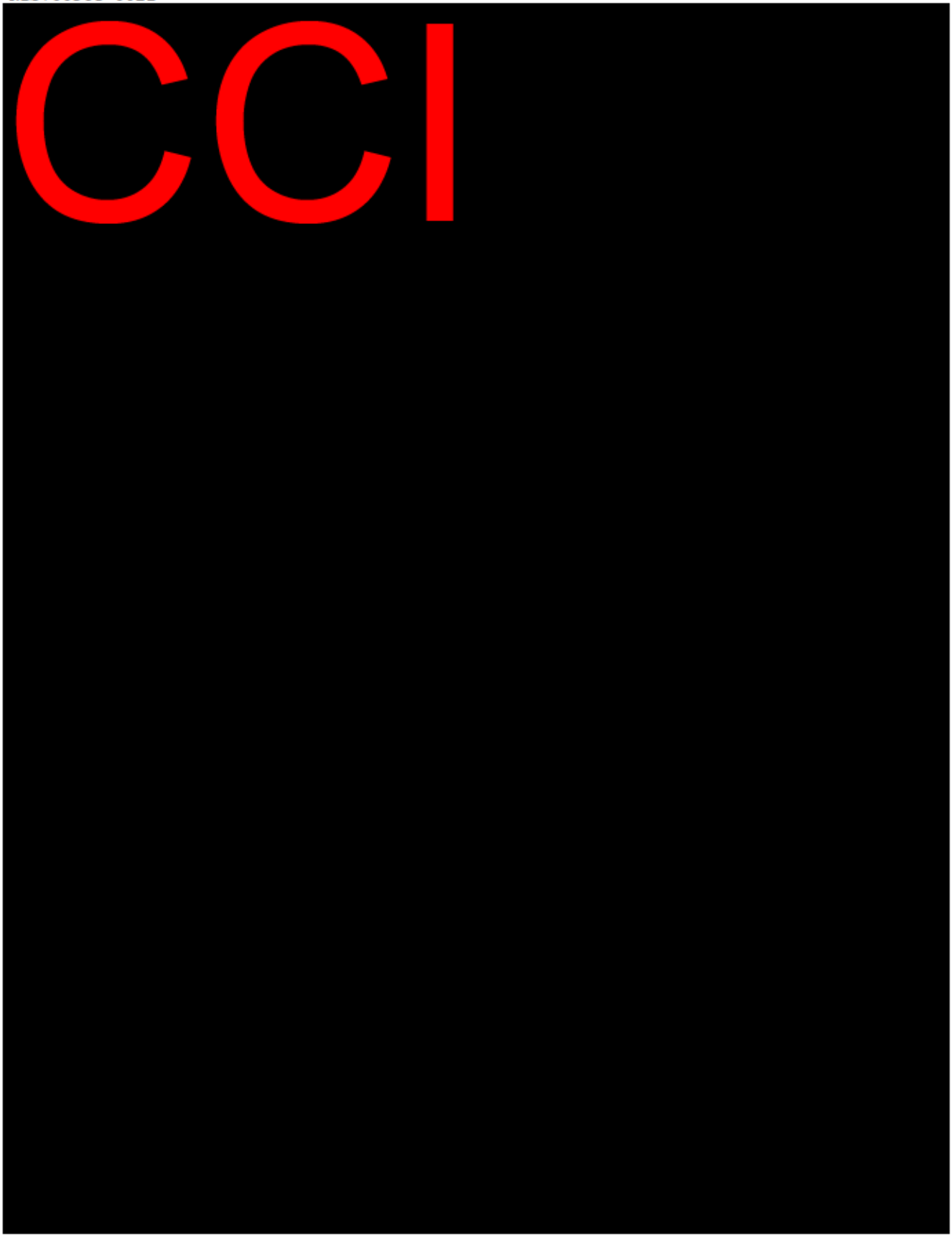
☐ Dissatisfied

☐ Somewhat Satisfied

☐ Satisfied

☐ Very Satisfied

☐ Extremely Satisfied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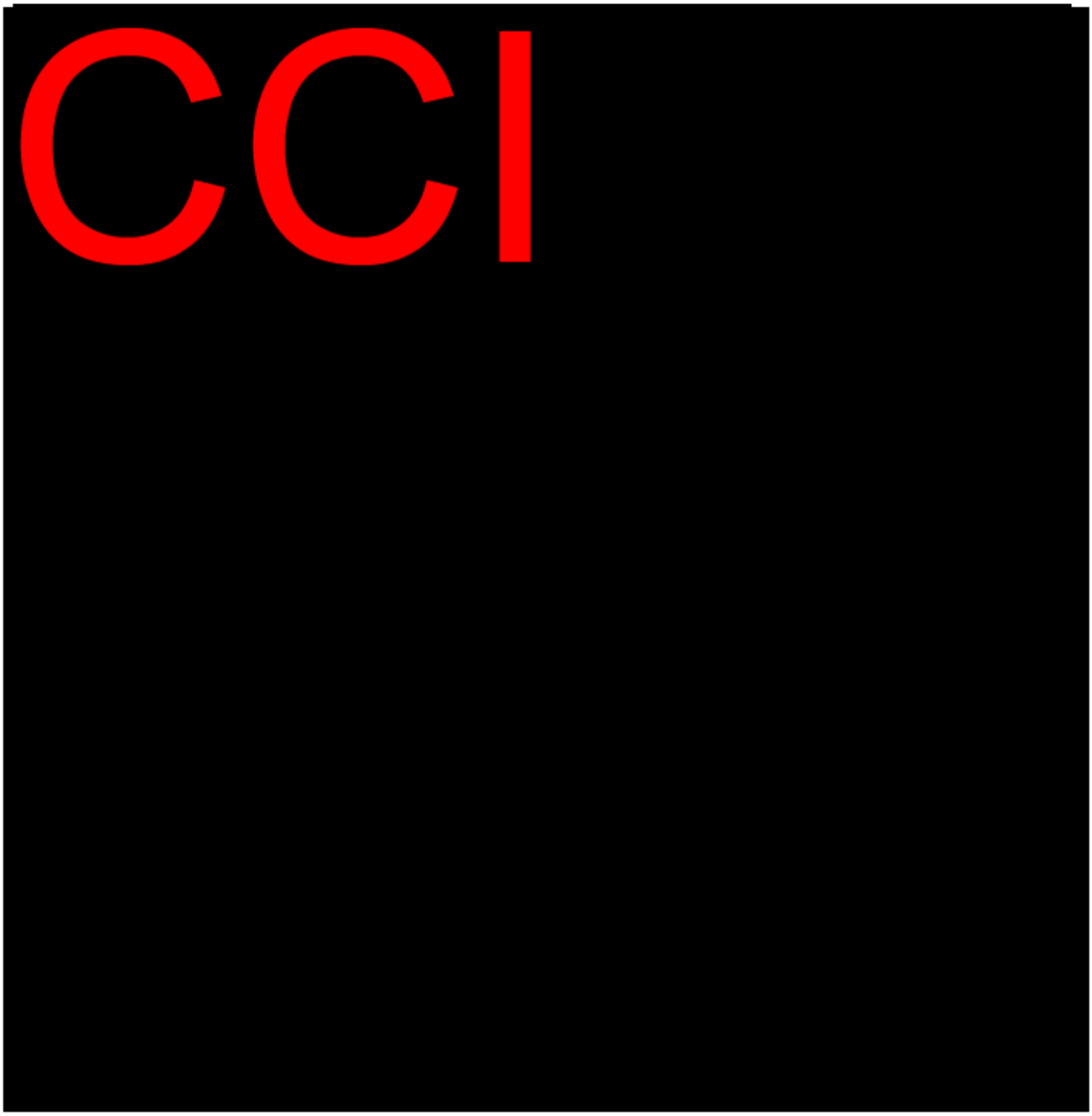
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12.12 Appendix 12: Personal Diary

This is an Example of Personal Diary:

Subject Diary Card: Week _____ to _____

Subject Initials:	*Subject Number:*

Dear Subject,

Please complete this diary card (with a pen) for each daily tablet intake of Mavenclad® and always take it with you to the hospital when you visit.

Please also remember to **bring your used and unused trial drug** with you in their original containers.

This diary has also been designed to help us follow your general health and any problem or discomfort you may experience while you are at home and to record all medication you take additionally to the trial drug.

If you have any problems please call your doctor or nurse:

Your contact person is: _____

Subject Trial Medication Record

Week	Date	Time (select am or pm)	Number of Tablets Taken	Batch # or Kit #	Comments
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
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12.14 Appendix 14: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A 2-year Prospective Study to Assess Health-related Quality of Life in Subjects with Highly-Active Relapsing Multiple Sclerosis Treated with Mavenclad®
EudraCT Number:	2017-002632-17
Clinical Trial Protocol Date / Version:	14 December 2018/ Version 2.0

Protocol Lead:

I approve t PPD PPD

Signature Date of Signature

Name: PPD

Function / Title: PPD

Institution: Merck KgaA

Address: Frankfurter Str. 250, Postcode: F135/101, 64293 Darmstadt, Germany

Telephone number: PPD

E-mail address: PPD

Signature Page –Coordinating Investigator

Trial Title:	A 2-year Prospective Study to Assess Health-related Quality of Life in Subjects with Highly-Active Relapsing Multiple Sclerosis Treated with Mavenclad®
EudraCT Number:	2017-002632-17
Clinical Trial Protocol Date / Version:	14 December 2018/ Version 2.0

I approve the design of the clinical trial and I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name: PPD

Function / Title: PPD

Institution: PPD

Address: PPD

Telephone number: PPD

E-mail address: PPD

Signature Page – Principal Investigator

Trial Title	A 2-year Prospective Study to Assess Health-related Quality of Life in Subjects with Highly-Active Relapsing Multiple Sclerosis Treated with Mavenclad®
EudraCT Number	2017-002632-17
Clinical Trial Protocol Date / Version	14 December 2018/ Version 2.0
Centre Number	
Principal Investigator	

I, the undersigned, am responsible for the conduct of the trial at this site and affirm that I understand and will conduct the trial according to the clinical trial protocol, any approved protocol amendments, International Conference on Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

I also affirm that I understand that Health Authorities may require the Sponsors of clinical trials to obtain and supply details about ownership interests in the Sponsor or Investigational Medicinal Product and any other financial ties with the Sponsor. The Sponsor will use any such information solely for the purpose of complying with the regulatory requirements. I therefore agree to supply the Sponsor with any necessary information regarding ownership interest and financial ties including those of my spouse and dependent children, and to provide updates as necessary to meet Health Authority requirements.

_____ _____

Signature Date of Signature

Name, academic degree:

Function / Title:

Institution:

Address:

Telephone number:

Fax number:

E-mail address:

Sponsor Responsible Persons not Named on the Cover Page

Name:	PPD
Function / Title:	Biostatistician
Institution:	Merck KGaA
Address:	Frankfurter Str. 250, 64293 Darmstadt, Germany
Telephone number:	PPD
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12.15 Appendix 15: Highly Effective Birth Control Methods

According to the HMA Clinical Trial Facilitation Group*, birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective. Such highly effective birth control methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
  - Oral
  - Intravaginal
  - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - Oral
  - Injectable
  - Implantable[2]
- Intra-uterine device[2]
- Intra-uterine hormone-releasing system[2]
- Bilateral tubal occlusion[2]
- Vasectomised partner[2,3]
- Sexual abstinence[4]

[1]Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method.

[2]Contraception methods that in the context of this guidance are considered to have low user dependency.

[3]Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the women of child-bearing potential (WOCBP)** trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4]In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.

*Clinical Trial Facilitation Group Final Recommendations related to contraception and pregnancy testing in clinical trials. Final Version 15 September 2014.

**A woman is considered of child-bearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

12.16 Appendix 16: Protocol Amendments and List of Changes

Protocol Amendment Summary of Changes and Overall Rationale for Amendment

Changes were made across various sections of the protocol for clarification of study conduct. The changes made are described in detail in the table below.

Section # and Name	Description of Change	Brief Rationale
1 Synopsis 2 Sponsor, Investigators and Trial Administrative Structure	Revised trial country list. Israel, Switzerland and Ireland were removed from the trial centres list and Slovakia was added.	The study is no longer conducted in these sites as a result of study feasibility assessments and hence they are removed from the list.
1 Synopsis	Change in the planned trial period. First subject first visit date was changed from Q1 2018 to Q2 2018 and last subject last visit date was changed to Q4 2021.	Based on the progress of the study these milestones for FSFV and LSLV were updated.
1 Synopsis	Secondary objective was revised to include term "highly active".	To clearly indicate the type of relapsing multiple sclerosis per the study design and to be consistent with the other sections.
1 Synopsis	Methodology section was revised to include the term "exploratory".	Term 'exploratory' in the section was added to clarify that the study is exploratory in nature.
1 Synopsis 4.1.1 Primary endpoint 4.2.1 Secondary endpoint CCI 8.0 Statistics	Section revised to clearly define endpoints. CCI revised to include "treatment effectiveness, side effects, and convenience assessed by TSQM at 6, 12 and 24 months". In addition, MSQoL-54 assessment schedule was updated to include 24 months.	The rationale was to clarify the scores that will be used for analysis as this was not specified before.
1 Synopsis 5.3.2 Exclusion criteria	Revised key exclusion criteria regarding immunosuppressive therapy to include mitoxantrone. In addition, sentences regarding hepatitis infection and PML were re-worded for clarity.	Per the SmPC, initiation of Mavenclad® is contraindicated in patients currently receiving immunosuppressive therapy.
1 Synopsis 8.0 Statistics	Section revised to clearly define end points, analysis sets and methods.	To clarify the scores that will be used for analysis as this was not specified before. In addition, analysis sets were added and defined in detail.
3.5 Scientific rationale for trial design	Subsection headings and further explanations on study drug, assessments and brain atrophy were added.	Section was restructured to clarify trial design.
5.1 Overall Trial design	Figure 1 updated to remove TSQM assessment from Baseline.	This change was made to be consistent with the trial procedure.
5.3.1 Inclusion criteria	Inclusion criterion number 5 was revised to introduce Appendix 15 which provides a list of highly effective birth control methods. In addition, definitions of WOCBP and postmenopausal women have been included and criterion 6 was combined with criterion 5.	In order to avoid possible human teratogenicity with the use of Mavenclad®, a list of highly effective birth control methods was provided to educate subjects participating in the study.

5.3.1 Inclusion criteria 7.4.3 Table 3 Local laboratory assessments 12.1 Appendix 1 Schedule of Assessments	Serology assessment for varicella added.	Inclusion criterion 7 was added to include subjects with previous exposure and immunity to varicella virus.
5.3.2 Exclusion criteria	Criteria 3: The phrase 'Presence or suspect of PML' was replaced with 'Presence of signs of PML detected by MRI, clinical and/or biomarker evaluations'. Criteria 7: Mitoxantrone was added to list of drugs Addition of new exclusion criteria 13	Revised the exclusion criteria 3 to include protocol approved procedures to evaluate the presence of PML Criteria 7: Per the SmPC, initiation of Mavenclad® is contraindicated in patients currently receiving immunosuppressive therapy. Criteria 13 was added to exclude subjects with moderate or severe hepatic impairment based on the safety profile of Mavenclad®.
5.5.1 Withdrawal from trial therapy	Removal of wording regarding 'anti-herpes prophylaxis'.	Removed due to incorrect placement of the text.
6 Investigational Medicinal Product and Other Drugs Used in the trial	General process of IMP provision and IRT contact was added.	In order to clarify the process by which the shipment is triggered after IRT contact.
6.5.4 Special precautions	Addition of subsection 6.5.4.1.	To clarify the process of switching from other DMDs to initiation of Mavenclad®.
6.12 Treatment of overdose	SAE report form replaced with eCRF report page wherever applicable.	In order to ensure proper documentation of the events eCRF page will be used in the study.
7.1.1 Screening 12.1 Appendix 1 Schedule of Assessments	Revised section to include method of subject ID assignment and screening period extension	Detailed information in the section was added to help clarify subject assignment and conditions for screening period extension in the study.
7.1.4 Baseline visit 7.3.2.1 TSQM v1.4 12.1 Appendix 1 Schedule of Assessments	Treatment satisfaction scoring (TSQM v1.4) deleted from Baseline visit.	TSQM is not to be administered to the subjects at Baseline visit, as subjects have not yet been dispensed nor administered with any trial medication.
7.1.7 Month 12 Visit 4 (±7 days)	Serology and safety analysis added for month 12 Text regarding split of Month 12 assessment added.	Missed statement was added per the Schedule of Assessments To define Month 12 and Month 12B assessment in detail.

7.3.5.2 Scanning: MRI scanning procedure	Name of the MRI scan user's manual was updated. General wording on scanning machine added. Safety assessment procedure added.	Image Acquisition Guidelines (IAG) is the name of the manual. To clarify usage of new equipment and To clarify the responsibility of central reader and investigator.
7.3.5.3 Evaluation of MRI Scans	Addition of new subsections as below 7.3.5.3.1 Disease diagnosis 7.3.5.3.2 MRI efficacy endpoints 7.3.5.3.3 Evaluation of Screening MRI scans for eligibility.	To include detailed explanation on the evaluation of MRI scans and to clarify the responsibility of site and investigator.
7.4.1.2, Methods of Recording and Assessing Adverse Events 7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities	Revised section to specify SAE reporting Heading changed from "Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities" to "Procedure for Reporting Serious Adverse Events".	SAEs must be reported by completing the eCRF SAE page and the Report Form is to be used only if the eCRF is not available. Adverse events of special interest and dose limiting toxicities are not applicable for this study
7.4.2 Pregnancy and In Utero Drug Exposure	Revised section to include appropriate reporting method as pregnancies are still reported using a paper form.	The process for SAE reporting is via eCRF whereas pregnancy is reported using a paper form.
7.4.3 Table 3 Local laboratory assessments	Revision of text for MRI assessment.	To clarify MRI screening procedure.
12.1 Appendix 1 Schedule of Assessments	Added legend for lymphocyte count Visit window aligned with section 7.1.5 Legend that states HRQoL / CCI [redacted] are "optional assessments, to be applied in subgroups, in centres familiarized in the respective scales" is deleted IRT assessment added Removed the word 'Urine' from pregnancy test and a legend added to include urine/serum for explanation.	Incorrectly added text was removed and all sections were aligned for consistency.
12.2 Appendix 2 MSQoL-54 scale to 12.12 Appendix 12 Personal diary	Replaced the word 'circle' with 'select'	Since the questionnaires will be completed electronically, 'circle' was replaced with 'select'
CCI [redacted]		
Section 12.15 Appendix 15 Highly effective birth control methods	The Appendix was provided to list highly effective birth control methods.	In order to avoid possible human teratogenicity with the use of Mavenclad®, a list of highly effective birth control methods was provided to educate subjects participating in the study.
	Some minor typos and inconsistencies were corrected in the protocol	

This amendment is substantial based on the criteria in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

Protocol History

Version Number	Type	Version Date
1.0	Original Protocol	19 September 2017
2.0	Amendment 1	14 December 2018

Protocol Version (2.0) (14 December 2018)