Clinical Trial Protocol

Clinical Trial Protocol Number	MS700568_0022
Title	A 2-year prospective study to evaluate the onset of action of Mavenclad ® in subjects with highly active relapsing multiple sclerosis
Phase	IV
IND Number	Not applicable
EudraCT Number	2017-002631-42
Coordinating Investigator	PPD PPD PPD PPD PPD Phone PPD Fax PPD
Sponsor	Merck KGaA Frankfurter Str. 250 64293 Darmstadt, Germany Medical Responsible: PPD PPD Telephone number: PPD email address: PPD
Clinical Trial Protocol Version	12 February 2019 / Version 2.0
Replaces Version	Not applicable

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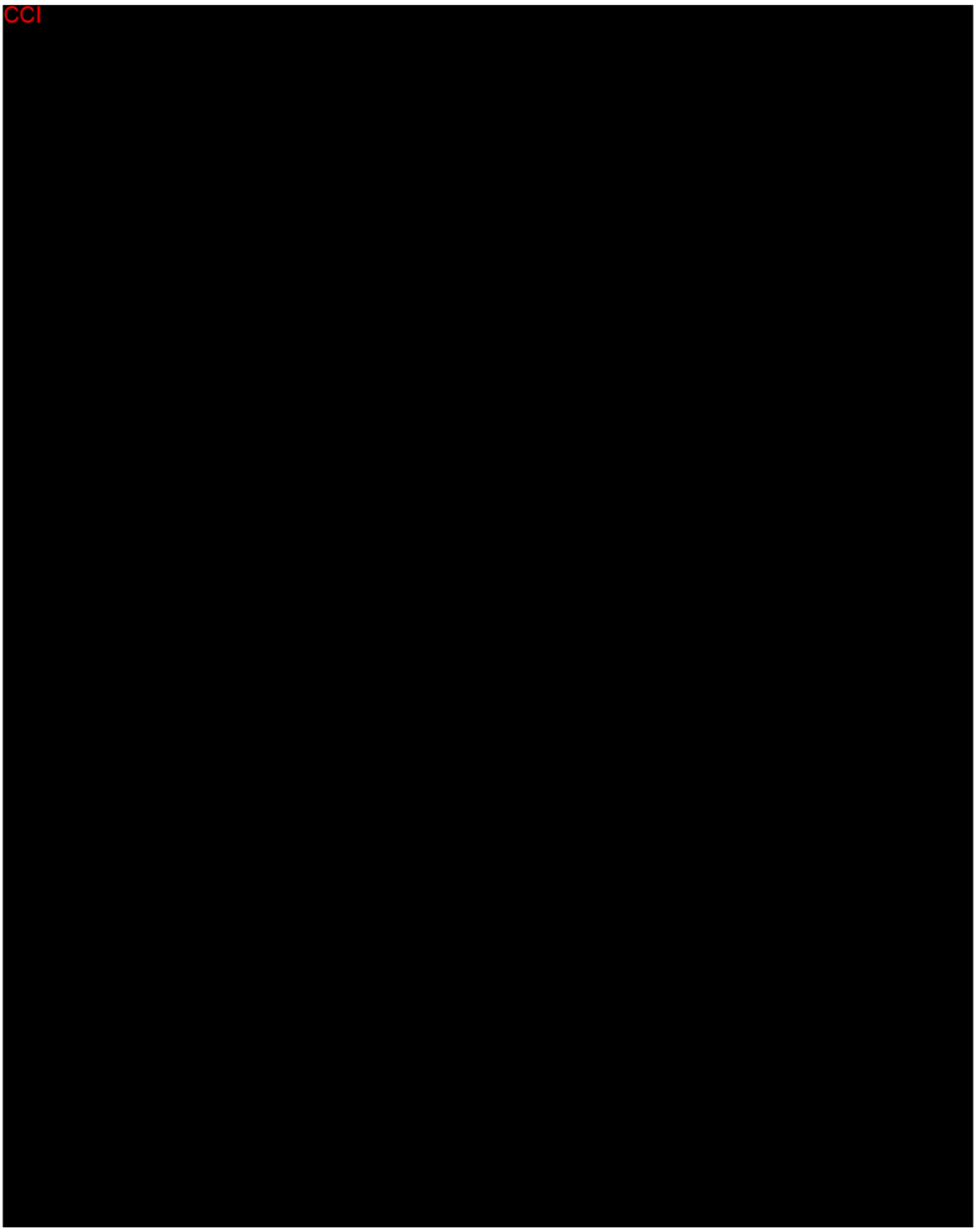

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List of Abbreviations

9HPT	9-Hole Peg Test
ACTH	Adrenocorticotropic hormone
AE(s)	Adverse Event(s)
ALT	Alanine Aminotransferase
ARR	Annualized Relapse Rate
CC	Complete-Case
CDMS	Clinically Definite Multiple Sclerosis
CI	Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organization
CCI	[redacted]
CT	Computed Tomography
CUA	Combined Unique Active
DMD	Disease Modifying Drug
CCI	[redacted]
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDSS	Expanded Disability Status Scale
FAS	Full Analysis Set
FDA	Food and Drug Administration
CCI	[redacted]
FS	Functional System
GCP	Good Clinical Practice
HIV	Human Immunodeficiency Virus
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INN	International Nonproprietary Names
IPMP	Integrated Project Management Plan
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intention-To-Treat
IUD	Intra-uterine Device
KFS	Kurtzke Functional System
MAR	Missing at Random
MCAR	Missing Completely at Random
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MTR	Magnetization Transfer Ratio
NEDA	No Evidence of Disease Activity

NEPAD	No Evidence of Progression or Active Disease
CCI	CCI
CCI	CCI
CCI	CCI
ON	Optic Neuritis
PML	Progressive Multifocal Leukoencephalopathy
PY	Patient Years
RMS	Relapsing Multiple Sclerosis
CCI	CCI
CCI	CCI
RRMS	Relapsing Remitting Multiple Sclerosis
SAE	Serious Adverse Event
SD	Standard Deviation
SDMT	Symbol Digit Modalities Test
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
T1 Gd+	T1 gadolinium-enhancing
T25FW	Timed 25-Foot Walk
TB	Tuberculosis
TEAE	Treatment-Emergent Adverse Event
TIW	Three Times a Week
VZV	Varicella Zoster Virus
WOCBP	Women of Childbearing Potential

1 Synopsis

Clinical Trial Protocol Number	MS700568_0022
Title	A 2-year prospective study to evaluate the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis
Trial Phase	IV
IND Number	Not applicable
FDA covered trial	Not applicable
EudraCT Number	2017-002631-42
Coordinating Investigator	PPD Phone PPD Fax PPD
Sponsor	Merck KGaA Frankfurter Str. 250 64293 Darmstadt Germany Medical Responsible: PPD PPD Phone: PPD
Sponsor Legal Representative in the European Union	Merck KGaA Frankfurter Str. 250 64293 Darmstadt Germany
Trial centers/countries	Approximately 80 trial sites across Europe (including, but not limited to Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Ireland, Italy, Poland, Spain, Sweden, the United Kingdom), as well as Australia, Canada and Israel.
Planned trial period (first subject in-last subject out)	First Patient First Visit: Q~~1~~2/2018 Last Patient Last Visit: Q~~3~~1/~~2021~~2022
Trial Registry	ClinicalTrials.gov EU Clinical Trials Register

Objectives:

Primary Objective:

- To determine the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis (RMS)

Secondary Objective:

- To assess the effect of Mavenclad® on different immune system composites in particular cell subtypes count and repopulation

Tertiary Objectives:

- To assess the safety and tolerability of Mavenclad®
- To assess the effect of Mavenclad® on progression of disability, cognition and incidence of relapse
- CCI

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Methodology:

This will be an open-label, single-arm, multicenter, 2-year Phase IV trial. Subjects meeting the eligibility criteria during a pre-baseline screening period of up to -3 months before baseline (Day 1 of treatment) will receive an initial treatment course in Year 1 and a retreatment course in Year 2.

Subjects will attend visits for assessments at end of Months 1,2,3,6, 12 following Baseline (Day 1 of treatment) and at end of Month 15,18, 24 following second treatment course (Month 1 of Year 2), respectively. Subjects will attend visits for blood sample as per mandatory monitoring at pre-Baseline and at Months 2, 6, 12, 14, 18 and 24. The primary endpoint(s) will be assessed during the first 6 months, secondary and tertiary endpoints will be assessed up to Month 24.

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Visit schedules for efficacy and safety assessments are detailed in the Schedule of Assessments.

Planned number of subjects: Approximately 265 subjects are planned to be included

Primary endpoint(s):

- Differences in the counts of combined unique active (CUA) MRI lesions during the first 6 months (i.e. during periods months 1-6, 2-6, 3-6) compared to baseline (i.e. the period screening to baseline)

Secondary endpoints:

- Characterization of immune cell subsets count at the end of 3, 6, 12, 15, 18 and 24 months compared to baseline

Tertiary endpoints:

Safety:

- Occurrences of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) including and up to 24 months

Clinical:

- Changes in Symbol Digit Modality Test (SDMT) outcome at the end of 6, 12, 18 and 24 months compared to baseline
- Disability evolution as measured by Expanded Disability Status Scale (EDSS)/ Kurtzke Functional System (KFS), 9-Hole Peg Test (9HPT), Timed 25-Foot Walk (T25FW) at the end of 6, 12, 18 and 24 months compared to baseline
- Annualized Relapse Rate (ARR) between baseline and 24 months
- Changes in CUA lesions during the following post-baseline periods –compared to baseline period (i.e. the period from screening to baseline):
  - Period of month 6 to month 12
  - Period of month 1 to month 12
  - Period of month 18 to month 24
  - Period of month 1 to month 24

  Further periods and comparisons may be defined in the SAP
- Number of CUA lesions during the baseline and post-baseline periods as defined above
- Changes in active T1 gadolinium (Gd)+ lesion count at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Volume changes of T1 Gd+ lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Number of T1 hypointense lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Change in volume of T1 hypointense lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Changes in new T2 lesion count during the post-baseline periods compared to the baseline period as defined above
- Responder rate during the different periods as defined above with responder being defined as subjects with a CUA lesion count reduction of at least 1
- Changes in T2 lesion volume at the end of 12 and 24 months compared to baseline
- Changes in Magnetization Transfer Ratio (MTR) at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Changes in brain volume at the end of 1, 2, 3, 6, 12 and 24 months compared to baseline (and changes at 24 months compared to 6 months to exclude pseudo-atrophy)
- No Evidence of Disease Activity (NEDA) at 24 months
- No Evidence of Progression or Active Disease (NEPAD) at 24 months

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Safety assessments: Safety assessments will include physical examination, including vital signs, 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 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:* • Previous exposure to drugs such as fingolimod, natalizumab, alemtuzumab, mitoxantrone and ocrelizumab • 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 with, e.g., monoclonal antibodies, methotrexate, cyclophosphamide, cyclosporine or azathioprine, or chronic use of corticosteroids • History of tuberculosis, presence of active tuberculosis, or latent tuberculosis • Presence of signs of PML detected by MRI, clinical and/or biomarker evaluations • Active malignancy
Investigational Medicinal Product: dose/mode of administration/dosing schedule: Mavenclad® 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 year. Each treatment week consists of 4 or 5 days on which a subject receives 10 mg or 20 mg (one or 2 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: The trial duration per subject will include: a pre-Baseline MRI assessment of up to 3 months and a 2-year treatment period.

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Primary endpoint analysis:

Differences in the counts of CUA lesions will be evaluated using a mixed-effects linear model, accounting for within-center/region correlation through a hierarchical model. The differences in the counts of CUA lesions during the 3 periods compared to the baseline period will be tested in a sequential order starting with the latest period. The 3 hypotheses will be tested one-sided on a 2.5% significance level. The testing procedure will stop as soon as one of the hypotheses cannot be rejected following the pre-specified order. Due to this sequential order of tests an adjustment for a potential type-I-error due inflation due to the multiple testing is not required. The full analysis set (FAS) will be the primary population.

Safety analysis:
All safety assessments will be summarized descriptively by the treatment group for the safety population.

2 Sponsor, Investigators and Trial Administrative Structure

The Sponsor of this open label, single-arm, Phase IV trial with Mavenclad® is Merck KGaA, Darmstadt, Germany.

The trial will be conducted at approximately 80 sites in Europe (including but not limited to Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Ireland, Italy, Poland, Spain, Sweden, the United Kingdom), as well as Australia, Canada and Israel.

The Coordinating Investigator, PPD represents all Investigators for decisions and discussions regarding this trial, consistent with the International Council for Harmonization (ICH) Topic E6 Good Clinical Practice (GCP); hereafter referred to as 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 presented in Appendix 14: Signature Pages and Responsible Persons for the Trial.

The trial will appear in the following clinical trial registries: ClinicalTrials.gov, EU clinical trials register.

A contract research organization (CRO) (PAREXEL International) 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 product (IMP) (cladribine) will be supplied by the Clinical Trial Supply Department of the Sponsor and packaged and labeled by Fisher Clinical Services.

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, 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 patients with MS (Oreja-Guevara C, 2015).

MS is a neurological disorder characterized by inflammatory demyelination and neurodegeneration in the central nervous system. Eight percent of patients 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, 2008). Early initiation of effective immunotherapy is considered to be important in this group of patients in order to prevent aggressive disease progression and severe disability accumulation (Dubey D, 2015).

3.2 Cladribine Tablets (Mavenclad®)

Despite the 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 (Tramacere, 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 patients across the spectrum of relapsing remitting multiple sclerosis (RRMS) (early to late stages, treatment naïve or -experienced subjects) (Giovannoni, 2010; Leist, 2014). In particular, it was found that treatment with oral cladribine resulted in significant improvements in clinical and radiological efficacy outcomes, with significantly more patients 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 G, 2011).

Cladribine is indicated for the treatment of adult patients with highly active relapsing MS as defined by clinical or imaging features:

- patients 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),
- patients with 2 or more relapses in the previous year, whether on DMD treatment or not

Efficacy data from the CLARITY trial showed statistically significantly improvements in the annualized relapse rate (ARR), proportion of patients relapse-free over 96 weeks, proportion of patients free of sustained disability over 96 weeks and time to 3-month EDSS progression in patient receiving cladribine 3.5 mg/kg compared to placebo (Giovannoni G, 2010). In addition, cladribine-treated group was statistically significantly superior to placebo with regard to number and relative reduction of T1 Gd+ lesions, active T2 lesions and combined unique active (CUA) lesions as demonstrated in brain MRI over the entire 96 weeks of the trial (Comi G, 2013).

3.3 Safety and Tolerability of Mavenclad®

The safety profile of Mavenclad® has been assessed in depth based on data from all studies of Mavenclad® in MS, including the long-term safety follow-up registry, and post-marketing data sources. Oral 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, after having accumulated more than 8,500 patient years (PY) of Mavenclad® exposure with up to 8 years of follow-up in some of the Mavenclad®-treated subjects, 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®, five 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 Risk-Benefit Assessment

The safety and tolerability of oral Mavenclad® in relapsing remitting MS have been demonstrated from the 2-year CLARITY trial followed by an additional 2.5 years of follow-up from the CLARITY-Extension (Cook S, 2016). While an oral formulation eliminates the adverse effects associated with frequent injections, Mavenclad® acts by depleting lymphocytes with a risk of developing opportunistic infections. The Sponsor have put in place adequate risk minimization measures for the participating subjects in this trial as well. Administering Mavenclad® will be restricted in subjects with lymphocyte count below normal in Year 1 and at least 800 cells/mm³ before initiating in Year 2. In addition, the lymphocyte count will be monitored at 2 and 6 months after each dosing schedule in Year 1 and Year 2. Subjects will be screened for latent TB infection as per local guidelines, as well as for Hepatitis B, Hepatitis C and human immunodeficiency virus (HIV) infection and will be excluded if found positive before each dosing schedule. The MRI scans will be evaluated by an expert to exclude any PML infection at screening and throughout the trial.

The risk-benefit relationship was carefully considered in the planning of the trial. The standard DMDs provide moderate efficacy and a low to moderate frequency of side effects. Second-line therapies for highly active MS are more effective, but associated with potentially severe side effects (Fazekas F, 2013). Mavenclad® is an oral drug approved in the treatment of highly active relapsing MS. Data from the CLARITY results suggest a clear benefit over placebo underlining the rationale for earlier treatment with cladribine tablets. In addition, data from CLARITY Extension indicates that treatment with cladribine tablets over 2 years, followed by 2 years of placebo, produced a durable clinical response (as measured from the end of CLARITY to the end of the Extension period). Importantly, there was no evidence of increased clinical activity (i.e., disease rebound) after treatment discontinuation (e.g. in the Cladribine 3.5 mg/kg switched to Placebo group), as reported for other therapies in MS with a direct effect on lymphocytes (Giovannoni G, 2017). The benefits of increased potential convenience and compliance with the unique posology of Mavenclad® will fill an unmet medical need in treating subjects with MS. The planned assessments for the trial are considered routine for monitoring MS disease progression and treatment outcomes. Standard of care will be provided to the subjects while undergoing the trial assessments to minimize clinical trial burden. MRI scanning with gadolinium enhancing contrast agents is routinely used for the identification and characterization of MS lesions (Rovira A, 2012). Monthly MRI assessment with gadolinium enhancing agent

have been used previously in Phase II trials with natalizumab (screening, Baseline and at the end of Months 1, 2, 3, 4, 5, 6, 9 and 12) (Miller, 2003) and fingolimod (Baseline and at the end of Months 1, 2, 3, 4, 5, 6 and 12) (Kappos, 2006); and in a Phase IIIb trial with interferon beta-1a (Baseline and at end of Months 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10) (De Stefano, 2010). A recent assessment by European Medicines Agency`s Pharmacovigilance Risk Assessment Committee (PRAC) concluded on the positive benefit risk outcome on gadolinium agents (gadobutrol, gadoteric acid and gadoteridol) with a recommendation to continue the use of such agents as per their current indications (EMA/424715/2017).

Based on the clinical and safety data available, the Sponsor considers that oral Mavenclad® has a positive benefit-risk profile that supports its use in the participating patient group. Therefore, the conduct of the trial specified in this protocol is considered justifiable. 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.

Refer to the Mavenclad® SmPC for further information about the nonclinical and clinical programs and Guidance for the Investigators.

This clinical trial will be conducted in compliance with the clinical trial protocol, ICH GCP and any additional applicable regulatory requirements.

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4 Trial Objectives

4.1 Primary Objective

- To determine the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis (RMS).

4.1.1 Primary Endpoint(s)

- Differences in the counts of CUA MRI lesions during the first 6 months (i.e. during periods months 16, 26, 36) compared to baseline (i.e. the period screening to baseline)

4.2 Secondary Objective

- To assess the effect of Mavenclad® on different immune system composites in particular cell subtypes count and repopulation

4.2.1 Secondary Endpoints

- Characterization of immune cell subsets count at the end of 3, 6, 12, 15, 18 and 24 months compared to baseline

4.3 Tertiary Objectives

- To assess the safety and tolerability of Mavenclad®
- To assess the effect of Mavenclad® on progression of disability, cognition and incidence of relapse

- CCI [redacted]

4.3.1 Tertiary Endpoints

Safety:

- Occurrences of treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs) including and up to 24 months

Clinical:

- Changes in Symbol Digit Modality Test (SDMT) outcome at the end of 6, 12, 18 and 24 months compared to baseline
- Disability evolution as measured by EDSS/KFS, 9-Hole Peg Test (9HPT), Timed 25-Foot Walk (T25FW) at the end of 6, 12, 18 and 24 months compared to baseline
- ARR between baseline and 24 months
- Changes in CUA lesions during the following post-baseline periods compared to baseline period (i.e. the period from screening to baseline):
  - Period of month 6 to month 12
  - Period of month 1 to month 12
  - Period of month 18 to month 24
  - Period of month 1 to month 24

  Further periods and comparisons may be defined in the SAP
- Number of CUA lesions during the baseline and post-baseline periods
- Changes in active T1 Gd+ lesion count at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Volume changes of T1 Gd+ lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Number of T1 hypointense lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Change in volume of T1 hypointense lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Changes in new T2 lesion count during the post-baseline periods compared to the baseline period as defined above
- Responder rate during the different periods as defined above with responder being defined as subjects with a CUA lesion count reduction of at least 1
- Changes in T2 lesion volume at the end of 12 and 24 months compared to baseline
- Changes in Magnetization Transfer Ratio (MTR) at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Changes in brain volume at the end of 1, 2, 3, 6, 12 and 24 months compared to baseline (and changes at 24 months compared to 6 months to exclude pseudo-atrophy)
- No Evidence of Disease Activity (NEDA) at 24 months
- No Evidence of Progression or Active Disease (NEPAD) at 24 months

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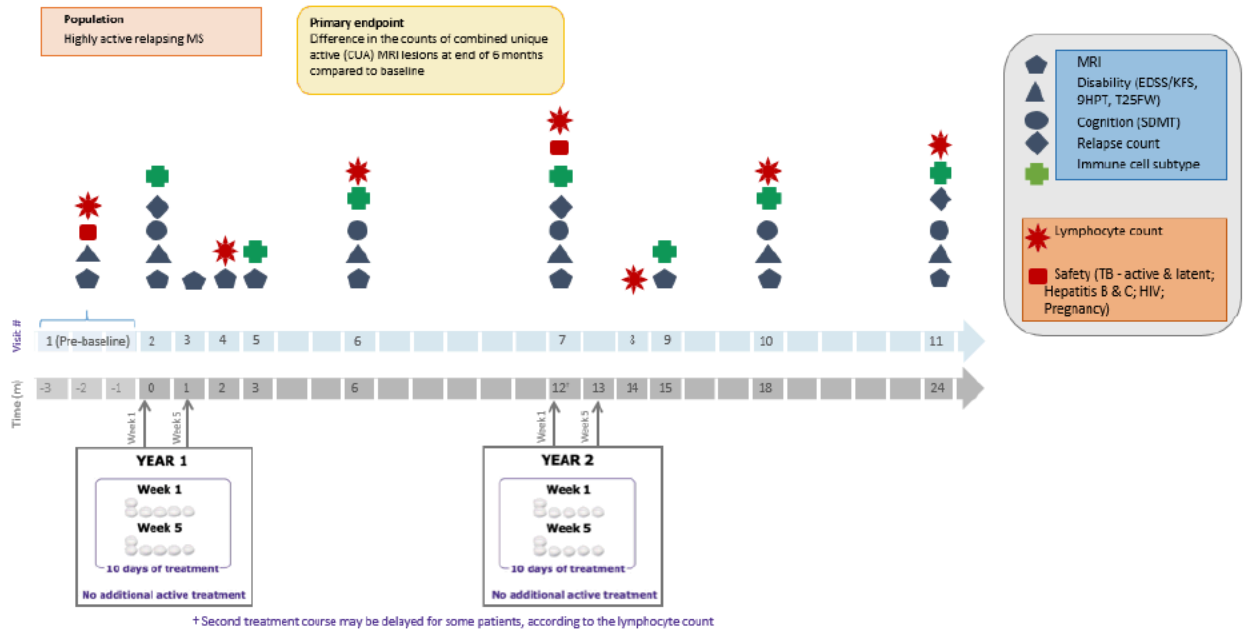
5 Investigational Plan

5.1 Overall Trial Design and Plan

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

Figure 1 Schematic of the Trial Design



Abbreviations: 9HPT=9-hole peg test; CUA=combined unique active; EDSS=expanded disability status scale; KFS= Kurtzke Functional System; HIV=human immunodeficiency virus; MRI=magnetic resonance imaging; SDMT=symbol digit modalities test; T25FW=timed 25-foot walk; TB=tuberculosis

A detailed schedule of trial procedures/assessments is provided in Appendix 1: Schedule of Assessments.

5.2 Discussion of Trial Design

This will be an open-label, single-arm, multicenter, 2-year Phase IV trial. This trial will include a pre-Baseline screening period up to -3 months prior to drug administration, followed by an initial treatment course in Year 1 and a retreatment course in Year 2. Baseline is defined as the day on which the first dose of Mavenclad® is administered. Subjects will attend visits for assessments at the end of Months 1, 2, 3, 6, and 12 following Baseline and at the end of Month 15, 18, 24 following second treatment course (Month 1 of Year 2), respectively. Subjects will attend visits for blood sample as per mandatory monitoring at pre-Baseline and at Months 2, 6, 12, 14, 18 and 24.

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.

Subjects with RMS will receive Mavenclad® 3.5 mg/kg body weight over 2 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. Each treatment week consists of 4 or 5 days on which a subject receives 10 mg or 20 mg (one or 2 tablets) as a single daily dose, depending on body weight as noted in SmPC (see Appendix 13: Mavenclad Posology).

MRI scans including lesion count, lesion volume, brain atrophy and MTR will be performed at screening, Baseline, and the end of Months 1, 2, 3, 6, 12, 15, 18, and 24. There will be a gap of at least 4 weeks between MRIs performed at screening and Baseline. Neurological examinations including EDSS/KFS, 9HPT, and T25FW will be performed at screening, Baseline, and the end of Months 6, 12, 18 and 24. SDMT will be performed at Baseline, and the end of Months 6, 12, 18 and 24. Blood specimens for immune cell subtypes count will be collected at Baseline, and the end of Months 3, 6, 12, 15, 18, 24. Physical examination including recording of vital signs will be performed at screening, Baseline, and Months 6, 12, 18 and 24. Safety laboratory tests including lymphocyte count, Hepatitis B and C, active and latent TB, HIV and urine/serum pregnancy test will be carried out at screening and before initiating second treatment course at Month 12; lymphocyte count will also be checked at 2 and 6 months after each treatment. If the absolute lymphocyte count at screening is done more than 4 weeks prior to Baseline, it should be repeated within 4 weeks of Baseline.

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

Following a relapse, subject may receive treatment with either acute short-term systemic corticosteroids or ACTH or plasma exchange at the discretion of the Investigator, following local good medical practice and international guidelines. A subject receiving any rescue medication with any other DMD will be followed-up by the investigator as standard of routine practise and will not participate further in any trial assessments; the subject should however complete the early termination visit for final assessment.

If a subject prematurely withdraws from the trial at any time, he/she will undergo all tests requested at the Early Termination visit as soon as possible.

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

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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 subjects meeting all inclusion criteria and no exclusion criteria will 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 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 12: Birth control methods which may be considered as highly effective). 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.
6. WOCBP must not be pregnant nor lactating or breast-feeding at Screening through at least 1 week after the last dose
7. 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.
8. 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. Previous exposure to drugs such as fingolimod, natalizumab, alemtuzumab, mitoxantrone and ocrelizumab
2. Hypersensitivity to Mavenclad® or to any of the excipients listed in the SmPC
3. Lymphocyte count not within normal limits of the local, hospital laboratory before initiation of first treatment course
4. 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

5. Positive for HIV
6. 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). 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
7. 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
8. Immunocompromised subjects, including subjects currently receiving immunosuppressive or myelosuppressive therapy with, e.g., monoclonal antibodies, methotrexate, cyclophosphamide, cyclosporine, or azathioprine, or chronic use of corticosteroids
9. 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
10. Subjects with hereditary problems of fructose intolerance
11. 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
12. Allergy or hypersensitivity to gadolinium and/or any other contraindication to perform an MRI
13. Moderate or severe renal impairment confirmed as per the standards of local clinical practice (for example, creatinine clearance <60 mL/min)
14. Moderate or severe hepatic impairment confirmed as per the standards of local clinical practice (for example, Child-Pugh score >6)
15. Subject is considered by the Investigator, for any reason, to be an unsuitable candidate for the trial.

5.4 Criteria for Initiation and Continuing of Trial Treatment

The lymphocyte count must be within normal limits before initiating treatment in Year 1, and at least 800/mm³ before initiating treatment 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 will not receive the trial treatment anymore.

5.5 Criteria for Subject Withdrawal

5.5.1 Withdrawal from Trial Therapy

Withdrawal may be considered in the following cases:

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

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
- Lost to follow-up
- Pregnancy
- Live or live attenuated vaccine at any time during the trial duration (except anti-herpes prophylaxis following a drop in lymphocyte count below 200 cells/mm³)
- Initiation of treatment with an experimental drug
- Initiation of treatment with another disease modifying therapy for multiple sclerosis
- Occurrence of active malignancies
- Presence of signs of PML detected by MRI, clinical and/or biomarker evaluations
- 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
- HIV infection, active tuberculosis and active hepatitis before initiation of second treatment course
- 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 center 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 cladribine tablets 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.

For subjects who experience a relapse and initiated on another DMD (as per investigator`s discretion), the subject will not participate further in any trial assessments and be followed-up by the investigator as standard of routine practice. The subject should however complete 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 CRF 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 an IMP or withdrawal of an 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 for a further 2 years (i.e., until 4 years 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 from these subjects for such purpose.

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. Month 1, and Month 12 visits are registered in the system.

6.1 Description of the Investigational Medicinal Product

The IMP is oral cladribine (tradename Mavenclad®).

Mavenclad® 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: hydroxypropyl betadex (2-hydroxypropyl-ß-cyclodextrin), sorbitol, magnesium stearate.

6.2 Dosage and Administration

The recommended cumulative dose of Mavenclad® is 3.5 mg/kg body weight over 2 years, and will be administered as 1 treatment course of 1.75 mg/kg per year. Full dosing and administration guidance can be found in the SmPC.

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.

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

6.5.1 Permitted Medicines

Since this is an outpatient trial, special care should be taken in the questioning of subjects regarding any self-medication. Subjects will also be provided with a diary form to record details of all concomitant medication use.

6.5.1.1 Disease Related

All concomitant medication used for conditions / symptoms related to MS (for example pain, fatigue or weakness, incoordination, bladder dysfunction, spasticity, depression 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 multiple sclerosis, with relapse criteria met (Section 7.3.3), treatment with either acute short-term systemic corticosteroids or ACTH or plasma exchange can be administered at the discretion of the Investigator, following local good medical practice and international guidelines. The Investigator must complete the evaluation prior to treatment with steroids or other therapeutic intervention(s) that may alter the subject's neurological state.

Upon Investigator's judgement, any relapse that is considered severe should be treated and followed up as per standard of routine practice. In case of subject receiving treatment with any

other DMDs, the subject will be discontinued from the trial and will not undergo any trial related scheduled assessments; the subject should however complete the early termination visit for final assessment.

The initiation of second treatment course with Mavenclad® following acute management of relapse will be at investigator discretion.

6.5.2 Prohibited Medicines

The following treatments are prohibited:

- Immunosuppressive or myelosuppressive therapy with, e.g., monoclonal antibodies, 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 cladribine 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

Subjects will be injected gadolinium contrast agent before each MRI assessment. For complete information on gadolinium contrast agent administration, refer to the locally approved labeling including the subject information leaflet.

The planned interventions for the trial are standard for monitoring MS disease progression and treatment outcomes.

6.5.4 Special Precautions

Follow special precautions as per the Mavenclad® SmPC.

6.5.5 Management of Specific Adverse Events or Adverse Drug Reactions

No specific measures are proposed for this trial. Standard medical care will be provided at the trial site for all AEs occurring during the trial. If lymphocyte counts drop below 200 cells/mm³, anti-herpes prophylaxis according to local standard practice should be considered during the time of grade 4 lymphopenia.

6.6 Packaging and Labeling of the Investigational Medicinal Product

Mavenclad® tablets will be supplied in blister packages, containing one, 4 and 6 tablets (to be confirmed by simulation and will for either 1-4-6 blister pack, 1-4 blister pack or 1-6 pack).

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 blister 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, 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.

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 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 depot, only if the local law requires.

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 electronic case report form (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 10: Example of Subject 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. After subjects leave the trial, medical care will be at the discretion of the Investigator following institutional or local standard of care.

Upon completion of trial, subjects will be offered the opportunity of enrolling into an Extension trial for a further 2 years (i.e., until 4 years from first treatment year course) (Section 5.8).

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.

Prior to performing any trial assessments not part of the subject's routine medical care, the Investigator will ensure that the subject has provided written informed consent according to the procedure described in Section 9.2.

A screening log will be completed for all subjects who sign the ICF but do not subsequently enter the trial. Subjects will be identified by their dates of birth; in addition, each subject's gender and reasons for exclusion from the trial will be recorded.

Study medication shall be administered over 2 years, one at the beginning of the first month and one at the beginning of the second month for each treatment year. The time and date of each tablet should be recorded by the subject in the diary card.

There will be a total of 11 visits during the whole trial period: one screening pre-Baseline visit, one Baseline visit, 3 visits each at 4-week interval during treatment year 1 (i.e., Months 1, 2, and 3), 2 visits each at 24-week interval during treatment year 1 (i.e., Month 6 and 12), 1 visit at 4-week interval during treatment year 2 (i.e., Month 14), 2 visits each at 12-week interval during treatment year 2 (i.e., Month 15 and 18) and a final visit at Month 24.

If eligible at screening subjects will then visit the trial center at Baseline (Day 1 of treatment) and Months 1, 2, 3, 6, 12, 14, 15, 18, 24. The Baseline visit will take place within 3 months from the screening visit (with a time window +7 days). There will be a gap of at least 4 weeks between

a MRI at screening and Baseline. All the subsequent visits shall have a time window of ± 7 days from the scheduled date of the visit.

Attempts should be made to conduct trial visits on the same day as the neurological exam and/or MRI, and/or blood sample collection. However, when this is not possible, a window of +/- 5 days will be allowed.

In case of acute relapse occurring anytime between signing of ICF and Baseline, the subject will be treated with either acute short-term systemic corticosteroids or ACTH or plasma exchange at the discretion of the Investigator, following local good medical practice and international guidelines and perform Baseline assessment at least 30 days after the last dose of steroids or ACTH or plasma exchange.

CCI [redacted]

When a subject has signed informed consent, a unique subject identification number will be assigned via IRT (Interactive Response Technology) consisting of 10 digits for the trial number, 3 digits for a site number and 4 digits for a sequentially assigned subject number (i.e., 0001, 0002, 0003, etc.).

Example: the fifth subject enrolled at Site 001 in protocol MS700568_0022 is assigned to the unique subject ID 70056800220010005:

Study No.	Site No.	Subject No.
7005680022	001	0005

CCI [redacted]

7.1 Schedule of Assessments

7.1.1 Pre-Baseline Screening (-3 months)

During the pre-Baseline screening visit, the prospective subject will be informed of the trial objectives and overall requirements, and written informed consent will be obtained prior to any trial specific assessments (see Section 9.2). The subject will then undergo a clinical MRI assessment centrally for disease activity and also to rule out PML. The read-out of this MRI scan to ensure compliance with the inclusion and exclusion criteria will be at investigator discretion (see Section 5.3).

A complete Screening Evaluation is to be performed during 3 months from Baseline, which will include the following assessments:

- Signing informed consent form
- Register IRT for shipment of medication to the site
- Demographic data, including date of birth, gender and race
- Medical history
- Disease history, including classification of disease, number of relapses within the past 12 months, treatment history, diagnosis date
- Review of inclusion/exclusion criteria
- Physical examination, including vital signs (including blood pressure, heart rate, temperature), height and weight
- Serology (HIV, Hepatitis C and B, and Varicella Zoster virus) and TB test
- MRI assessment (see Section 7.3.1)
- Neurological assessment including EDSS/KFS, 9HPT and T25FW (excluding SDMT) (see Section 7.3.2)
- The contraceptive method used will be recorded, or, alternatively, if applicable, the age at menopause will be documented
- Blood samples for safety analysis at local laboratory (see Section 7.4.3)*.
- Urine pregnancy test (for female subjects of child-bearing potential only) at local laboratory**
- Assessment of AEs, concomitant medications and concomitant procedures

*** If the local laboratory blood at the Screening visit is conducted within 10 days of Study Day 1, no blood samples need to be repeated at Study Day 1.**

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

As this is a frequent MRI trial, best results would be obtained if subjects would not receive, for at least the initial 12 weeks of the trial, any treatment with oral or systemic corticosteroids or any standard treatment as per local guidelines in the event of MS clinical attacks. However, since this may raise ethical concerns, every treatment must be reported by the treating physician to permit a subgroup analysis of those subjects, and specific restrictions will be applied for the MRI assessment (Section 7.3.1.1).

Subjects who do not meet the inclusion/exclusion criteria within the specified time limits (i.e., 3 months prior to drug administration) and fail screening 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. Such re-screened subjects will undergo complete screening assessments.

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.

7.1.2 Treatment Period

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

7.1.3 Baseline Visit (Study Day 1) (+7 days)

Once a subject has met the eligibility criteria and is ready to begin treatment, he/she will be administered the IMP. Baseline is defined as the day on which the first dose of IMP is administered (Day 1 of treatment).

The following procedures will be performed at Baseline:

- Review of inclusion/exclusion criteria
- Review of subject diary
- Physical examination* including vital signs (including blood pressure, heart rate, temperature)
- MRI assessment** (see Section 7.3.1)
- Neurological examination including SDMT, EDSS/KFS, 9HPT and T25FW***
- Number of relapses within the last 12 months (see Section 7.3.3)
- CCI [redacted]
- Urine pregnancy test (for female subjects of child-bearing potential only)
- Administration of trial medication
- Assessment of AEs, concomitant medications and concomitant procedures
- Weight measurement and assignment of IMP via IRT

*** 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)

**** There will be a gap of atleast 4 weeks between a MRI at screening and Baseline. MRI scans will be assessed for efficacy and safety purposes.**

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

If the lymphocyte count at screening is done before 4 weeks from Baseline, it should be repeated within 4 weeks of 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 10: Example of Subject 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.

7.1.4 Month 1 Visit (±7 days)

The following procedures and assessments will be performed at the Month 1 visit:

- Review of subject diary
- Weight measurement and assignment of IMP via IRT
- MRI assessment (see Section 7.3.1)
- Administration of trial medication
- Assessment of AEs, concomitant medications and concomitant procedures

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 (±7 days)

The following procedures and assessments will be performed at the Month 2 visit:

- Review of subject diary
- MRI assessment (see Section 7.3.1)
- Assessment of AEs, concomitant medications and concomitant procedures
- Blood samples for safety analysis at local laboratory*

*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 3 Visit (±7 days)

The following procedures and assessments will be performed at the Month 3 visit:

- Review of subject diary
- MRI assessment (see Section 7.3.1)

CCI [redacted]

- Assessment of AEs, concomitant medications and concomitant procedures

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 6 Visit (±7 days)

The following procedures and assessments will be performed at the Month 6 visit:

- Review of subject diary
- Physical examination including vital signs (including blood pressure, heart rate, temperature)
- MRI assessment (see Section 7.3.1)
- Blood samples for safety analysis at local laboratory *
- Neurological examination including SDMT, EDSS/KFS, 9HPT and T25FW

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.

7.1.8 Month 12 Visit (±7 days)

The following procedures and assessments will be performed at the Month 12 visit:

- Review of subject diary
- Physical examination including vital signs (including blood pressure, heart rate, temperature)
- Serology (HIV, Hepatitis C and B) and TB test
- MRI assessment (see Section 7.3.1)
- Neurological examination including SDMT, EDSS/KFS, 9HPT and T25FW
- Number of relapses (see Section 7.3.3)
- Blood samples for safety analysis at local laboratory (Section 7.4.3)*

CCI [redacted]

- Urine pregnancy test (for female subjects of child-bearing potential only)
- Administration of trial medication and provision of trial medication intake for Month 13
- Weight measurement and assignment of IMP via IRT
- Assessment of AEs, concomitant medications and concomitant procedures

*Lymphocyte count should be at least 800 cells/mm³ before initiating cladribine 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 cladribine anymore.

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.

7.1.9 Month 14 Visit (±7 days)

- Review of subject diary
- Blood samples for safety analysis at local laboratory*
- Assessment of AEs, SAE's 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.

7.1.10 Month 15 Visit (±7 days)

The following procedures and assessments will be performed at the Month 15 visit:

- Review of subject diary

- MRI assessment (see Section 7.3.1)

CCI [redacted]

- Assessment of AEs, concomitant medications and concomitant procedures

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.

7.1.11 Month 18 Visit (±7 days)

The following procedures and assessments will be performed at the Month 18 visit:

- Review of subject diary
- Physical examination including vital signs (including blood pressure, heart rate, temperature)
- MRI assessment (see Section 7.3.1)
- Neurological examination including SDMT, EDSS/KFS, 9HPT and T25FW

CCI [redacted]

- Blood samples for safety analysis at local laboratory*
- 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.

7.1.12 Final Visit / Early Termination (Month 24 Visit [±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:

- Review of subject diary
- Physical examination including vital signs (including blood pressure, heart rate, temperature)
- MRI assessment (see Section 7.3.1)
- Neurological examination including SDMT, EDSS/KFS, 9HPT and T25FW.
- Number of relapses (see Section 7.3.3)

- Blood samples for safety analysis (only lymphocyte count) at local laboratory (see Section 7.4.3)

CCI [redacted]

- Assessment of AEs, concomitant medications and concomitant procedures

7.1.13 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 additional neurological evaluations following a relapse (see Section 7.3.3). The data from unscheduled visits will be collected in the eCRF.

7.2 Demographic and Other Baseline Characteristics

At screening, the following demographic data will be collected: date of birth, sex (gender), race, ethnicity. Full details of the various assessments are detailed in Section 7.1.

7.3 Efficacy Assessments

7.3.1 MRI

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

7.3.1.1 Schedule

MRI scans will be assessed at the Pre-Baseline Screening, Baseline and at Months, 1, 2, 3, 6, 12, 15, 18 and 24 (see Appendix 1: Schedule of Assessments).

Restrictions for the MRI schedule:

In order to prevent interferences caused by steroid or ACTH administration or by relapse, the following restrictions will apply:

- For any relapse occurring within the first 6 months that may require a steroid or ACTH treatment, the next MRI should be brought forward before initiation of steroid or ACTH treatment as long as the time since the previous MRI is at least 4 weeks.

- For any relapse occurring within the first 6 months and a steroid or ACTH treatment is already initiated (without possibility of bringing forward the next MRI), the planned MRI should be postponed up to at least 14 days from last dose of steroid/ACTH treatment.

- For any relapse occurring after 6 months that may require a steroid or ACTH treatment / a steroid or ACTH treatment is already initiated, as the visit intervals are long (visit at end of months 6, 12, 15, 18, 24), the next MRI should be planned as scheduled and at least occurring after 30 days of last dose of steroid/ACTH.

7.3.1.2 Scanning: MRI Scanning Procedure

MRI measures of white matter lesional activity (i.e., new/enlarging T2 lesions, T1 hypointense or Gd-enhancing T1 lesions) and those of brain atrophy (i.e., percentage of brain volume change) have shown to be valid surrogate endpoints for clinical outcomes. Advanced MRI techniques, such as MTR may provide higher pathological specificity for the more destructive aspects of the disease (i.e., demyelination and neuroaxonal loss) and be more closely associated with clinical correlates (Wattjes MP et al, 2015).

The principal primary outcome measure will be the number of CUA lesions. CUA lesions, which combines the high sensitivity of T1 activity with the greater specificity for permanent lesions of T2 activity, has been chosen as the best single indicator of MS activity. The following MRI parameters will be measured for all subjects for each scan obtained during the trial:

- Active lesions defined as T1 gadolinium-enhancing lesions, or new T2 non-enhancing or enlarging T2 lesions during each pre-defined period (designated "CUA MRI lesions")
- T1 hypointense lesions
- Brain volume
- MTR

The MRI scan will also be evaluated for safety assessment to rule out PML or any serious central nervous system disease (e.g., tumor, stroke etc).

All scans will be performed according to a standard protocol detailed in a separate MRI scan user's manual. A central imaging core lab will perform the analysis of all MRI scans. 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.

Prior to subject assessment, each trial site will be asked to send a 'test' or 'dry-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, will sites be allowed to begin assessing subjects.

Each subject should be scanned using the same machine throughout the trial.

7.3.1.2.1 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 center 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.

7.3.1.3 Evaluation of MRI Scans

The CUA lesions and all other secondary MRI variables will be evaluated by the central imaging core lab.

7.3.2 Clinical Assessments

At visits where both neurological examination and an MRI are scheduled, every attempt to conduct both assessments on the same day should be made by the same investigator. However, in circumstances this is not possible, a window of +/-5 days is permissible. Prior to each neurological assessment, the Investigator should not refer to previous neurological assessments carried out on that subject.

7.3.2.1 Symbol Digit Modalities Test (SDMT)

Brief and easy to administer, the SDMT has demonstrated remarkable sensitivity in detecting the presence of brain damage as well as changes in cognitive functioning over time and in response to treatment (Benedict RHB et al, 2017). The SDMT involves a simple substitution task whereby, using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. There is a single outcome measure – the number correct over the 90 sec time span. A re-arrangement of the key at each visit will be applied to minimize practise effect (Roar M et al, 2016).

The SDMT assessment is a tertiary outcome of this trial and will be administered as part of Baseline and at the end of 6, 12, 18 and 24 months. The SDMT will be performed before administration of Mavenclad® tablets at Baseline and month 12.

7.3.2.2 Expanded Disability Status Scale (EDSS)/Kurtzke Functional System (KFS)

The neurological examination, EDSS/KFS will be obtained at the Pre-Baseline, Baseline, and at the end of 6, 12, 18 and 24 months (see Appendix 7: Kurtzke Functional System, and Appendix 8: Expanded Disability Status Score (EDSS)).

Definition of EDSS Progression

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

- If the Baseline EDSS score is 0, the increase must be ≥ 1.5 units
- If the Baseline EDSS score is ≥ 0.5 or ≤ 4.5, the increase must be ≥ 1.0 units
- If the Baseline EDSS score ≥ 5.0 the increase must be ≥ 0.5 units

A confirmed EDSS progression is defined as EDSS progression (as defined above) confirmed after 3 months.

7.3.2.3 9-Hole Peg Test (9HPT)

The 9-Hole Peg Test (9HPT) is considered as a gold standard measure of manual dexterity and most frequently used in MS research and clinical practice. The 9HPT requires participants to repeatedly place and then remove nine pegs into nine holes, one at a time, as quickly as possible (Feys P et al, 2017). The 9HPT should be completed at Pre-Baseline, Baseline and then at the end of Months 6, 12 18, and 24 to measure the level of disability over time.

7.3.2.4 Timed 25-Foot Walk (T25FW)

The T25FW is considered the best characterized objective measure of walking disability and can be used across a wide range of walking disabilities in MS. The subject is instructed to walk as fast and safely as possible (i.e., maximal walking speed) across a clearly marked, linear 25-foot or 7.62-m course. There are no turns in the course, and the T25FW starts with a static start (i.e., standing upright and still). The subject may use an assistive device. The subject is timed walking the 25-foot course twice, and T25FW score is the average in seconds of the two successive trials (Motl RW, 2017).

The T25FW should be completed at Pre-Baseline, Baseline and then at the end of Months 6, 12 18, and 24 to measure the level of disability over time.

7.3.3 Relapse Evaluation

Relapse evaluation will be completed at Baseline, end of Month 12 and 24 or following early termination and whenever necessary.

Note that this section defines relapse as a variable to be measured during the course of the trial.

All the following criteria are to be met for establishing an MS clinical relapse:

1. Neurological abnormality, either newly appearing or re-appearing, with abnormality specified by both

    a. Neurological abnormality separated by at least 30 days from onset of a preceding clinical event,

    and

    b. Neurological abnormality lasting for at least 24 hours

2. b) Absence of fever or known infection (fever with temperature (axillary, orally or intrauricularly) > 37.5°C / 99.5 °F)

3. Objective neurological impairment, correlating with the subject's reported symptoms, defined as either

    a. Increase in at least one of the functional system (FS) scores of the EDSS

    or

    b. Increase of the total EDSS score

The occurrence of paraesthesia, fatigue, mental symptoms, and/or vegetative symptoms without any additional symptom will not be classified as an MS clinical relapse.

7.3.3.1 Procedure for Relapse Evaluation

The subject will be instructed to contact immediately the treating physician if he/she develops new or re-occurring or worsening neurological (including visual) symptoms. At each scheduled visit, the subject will be asked whether any such symptoms have occurred.

Upon reporting symptoms indicative of a relapse, the investigator will assess whether the symptoms occur in the presence of fever or infection (in case of an unscheduled phone-contact, the treating physician may simply ask the subject). If fever or infection is excluded, the Investigator must arrange for a neurological examination as soon as possible, at the latest within 7 days following the reporting of the event. If fever or infection cannot be excluded, the neurological examination by the Investigator will have to be postponed until the fever or the infection have ceased (provided, that the symptoms indicative of a relapse are still present).

Based on the respective EDSS/KFS scores, in conjunction with the results from previous examinations, the Investigator will assess whether the EDSS criterion for a relapse during the course of the trial is fulfilled.

Note: Since relapses may impact on the results of MRI scans, the occurrence of a relapse may cause the postponement of MRI scans (Section 7.3.1).

7.3.4 No Evidence of Disease Activity (NEDA)

NEDA, also referred to as freedom from disease activity, is a new goal that is emerging in MS treatment. NEDA is a composite measure of disease activity, including relapses, cognition & disability progression (measured by the Expanded Disability Status Scale (EDSS)), and MRI activity.

7.3.5 No Evidence of Progression or Active Disease (NEPAD)

NEPAD is a composite measure of disease activity, an evolution of NEDA including relapses, cognition & disability progression and MRI activity.

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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). The reporting period for AEs is described in Section 7.4.1.3.

7.4.1 Adverse Events

7.4.1.1 Adverse Event Definitions

Adverse Event

An adverse event (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 eCRF SAE 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 in Section 7.1.12.

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

7.4.1.4 Procedure for Reporting Serious Adverse Events, Adverse Events of Special Interest and Dose Limiting Toxicities

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 eCRF SAE page 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 (see Section 7.4.1.3) and are assessed for final outcome at the End of Treatment visit (see Section 7.1.12). All SAEs ongoing at the End of Treatment/Early termination 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 email immediately (within a maximum of 24 hours after being 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

Blood samples will be collected for the following clinical laboratory tests, following the timing noted in the Schedule of Assessments (Appendix 1: Schedule of Assessments) and sent to the central laboratory for analysis (Section 7.3.6). All samples should be clearly identified.

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Local clinical laboratory samples will be collected for screening, post-treatment effect 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**
	Per local guideline, imaging and/or blood test: Chest X-ray, chest CT scan, MRI and/or positive QuantiFERON-TB Gold test and/or skin test	TB (active and/or latent)
	MRI	PML and EC/IC
	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
	Serology	Hepatitis B, Hepatitis C, HIV
	Per local guideline, imaging and/or blood test: Chest X-ray, chest CT scan, MRI and/or positive QuantiFERON-TB Gold test and/or skin test.	TB (active and/or latent)
	Urine and/or serum tests	Pregnancy

Abbrevations: CT=computed tomography; HIV=human immunodeficiency virus; MRI=magnetic resonance imaging; PML=progressive multifocal leukoencephalopathy; EC/IC=exclusion criteria/inclusion criteria; TB=Tuberculosis; VZV=Varicella Zoster virus

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

The total blood volume that will be collected at each visit from each subject for the above mentioned assessments is described in Appendix 9: Blood Volumes.

7.4.4 Vital Signs, Physical Examinations, and Other Assessments

Vital signs including body temperature, respiratory rate, and heart rate (after 5-minute rest) will be measured once at Screening and throughout the trial at the visits indicated in the Schedule of

Assessments. Arterial blood pressure (after 5-minute rest) will be measured twice using a validated device and recorded at the visits indicated in the Schedule of Assessments (Appendix 1: Schedule of Assessments).

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 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.

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8 Statistics

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8.2 Randomization

Not applicable.

8.3 Endpoints

8.3.1 Primary Endpoint(s)

- Differences in the counts of CUA MRI lesions during the first 6 months (i.e. during periods months 1-6, 2-6, 3-6) compared to baseline (i.e. the period screening to baseline).

8.3.2 Secondary Endpoints

- Characterization of immune cell subsets count at the end of 3, 6, 12, 15, 18 and 24 months compared to baseline

8.3.3 Tertiary Endpoints

Safety:

- Occurrences of TEAEs and SAEs including and up to 24 months

Clinical:

- Changes in SDMT outcome at the end of 6, 12, 18 and 24 months compared to baseline
- Disability evolution as measured by EDSS/KFS, 9HPT, T25FW at the end of 6, 12, 18 and 24 months compared to baseline
- ARR between baseline and 24 months
- Changes in CUA lesions during the following post-baseline periods compared to the baseline period (i.e. the period from screening to baseline):
    - Period of month 6 to month 12

- Period of month 1 to month 12
- Period of month 18 to month 24
- Period of month 1 to month 24

Further periods and comparisons may be defined in the SAP

- Number of CUA lesions during the baseline and post-baseline periods as defined above
- Changes in active T1 Gd+ lesion count at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Volume changes of T1 Gd+ lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Number of T1 hypointense lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Change in volume of T1 hypointense lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Changes in new T2 lesion count during the post-baseline periods compared to the baseline period as defined above
- Responder rate during the different periods as defined above with responder being defined as subjects with a CUA lesion count reduction of at least 1
- Changes in T2 lesion volume at the end of 12 and 24 months compared to baseline
- Changes in MTR at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline
- Changes in brain volume at the end of 1, 2, 3, 6, 12 and 24 months compared to baseline (and changes at 24 months compared to 6 months to exclude pseudo-atrophy)
- NEDA at 24 months
- NEPAD at 24 months

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8.4 Analysis Sets

The following analysis sets are defined:

- Enrolled Set: all subjects who provided informed consent
- ITT (intent-to-treat) Set: all subjects classified as eligible
- FAS (Full Analysis Set): all subjects from the ITT who received at least one dose of the 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 who have received at least one dose of the trial treatment.

The primary analysis and all efficacy analyses will be performed on the FAS. As a robustness analysis the primary analysis will be repeated on the ITT (if different from the FAS) and the Treatment Completer Sets. 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

8.5.1 General Considerations

All analyses of all endpoints except the primary analysis, will be performed exploratively and, differences with a p-value of 0.05 or less will be considered nominally statistically significant.

Parameter estimates with associated 95% confidence intervals (CIs) will be reported in each analysis. No correction for multiple testing will be applied for any secondary or tertiary 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 secondary and tertiary analysis set concerns repeated measurements of outcomes for each individual, it is likely that observations pertaining to each individual will be correlated. Furthermore, as this is a multi-center 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-center correlation (Gibbons, 2010).

The parametric assumptions underlining the regression models specified will be examined. Should these assumptions be violated, alternative methods, such as non-parametric approaches, may be considered in addition.

Assessment Schedules

It is likely that the second year treatment may be delayed substantially due to grade 3 or 4 lymphopenia 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 efficacy analyses.

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.

In addition to the primary analysis model which is assuming missing at random (MAR), multiple imputation methods assuming different patterns of missingness will be applied to evaluate the robustness of results (see Section Robustness Analyses for more details).

8.5.2 Analysis of Primary Endpoints

The primary endpoint(s) for the trial are differences in counts of CUA MRI lesions during the first 6 months compared to baseline, i.e. the following differences will be evaluated:

- Period of month 3 to month 6 compared to the baseline period (i.e. the period of screening to baseline).
- Period of month 2 to month 6 compared to the baseline period,
- Period of month 1 to month 6 compared to the baseline period.

The differences in counts of CUA lesions will be evaluated using a mixed-effects linear model, accounting for within-center/region correlation through a hierarchical model.

The analysis will also adjust for baseline factors deemed to be prognostic for the primary endpoint, as judged by clinical experts:

- CUA lesion count during the baseline period,
- age,
- EDSS (≤3/>3).

The analysis will also adjust for the difference length and number of MRIs of the periods to be compared.

The difference in the counts of CUA lesions during the 3 periods compared to the baseline period will be tested in a sequential order. The 3 hypotheses are defined as follows:

H_{0i}: Δ CUA(t_i) ≥ 0 vs H_{1i}: Δ CUA(t_i) < 0, i=1,2,3

with

$\Delta CUA(t_i) = \#CUA(p_i) - \#CUA(p_0)$, i=1,2,3,

$\#CUA(p_i)$: count of CUA lesions during period p_i, i=0,1,2,3,

p_0: baseline period (period screening to baseline),

p_i: period month i to month 6, i=1,2,3.

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

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

The 3 hypotheses will be tested one-sided on a 2.5% significance level. The testing procedure will stop as soon as one of the hypotheses cannot be rejected following the pre-specified order. Due to this sequential order of tests an adjustment for a potential type-I-error due inflation due to the multiple testing is not required.

An estimate for the difference in CUA lesions duringthe specified periods compared to the baseline period will be reported, together with one-sided p-values. In addition, 95% CI and two-sided p-values will be presented to allow for comparison with the two-sided secondary and tertiary analyses.

Robustness Analyses

The robustness of the primary analysis model will be evaluated by repeating the analysis using generalized model assuming a negative binomial distribution.

In order to evaluate the robustness of the assumption that missing data are observed at random (MAR), the primary analysis will be repeated applying a pattern mixture model. If missingness can be considered MAR (e.g. MRI missing for technical reasons), data will be imputed by multiple imputation from post-baseline data while if considered not missing at random (MNAR) (e.g., drop-out due to lack of efficacy), data will be imputed from baseline data. The propensity score method based on CUA lesion count during the baseline period, age, and EDSS will be applied.

8.5.3 Analysis of Secondary and Tertiary Endpoints

Analysis comparing continuous secondary and tertiary endpoints measured repeatedly at specific time points to baseline will be undertaken using similar techniques to those outlined for the primary analysis while taking the within-subject correlation into account where appropriate. Linear regression modelling assumes that outcomes are normally distributed. Appropriate transformations (such as square root or log transform) may be used to achieve normality. Alternatively, nonparametric methods may be applied.

Annualized relapse rate will be evaluated using a Poisson regression model with count of relapses as dependent variable and with age and EDSS as covariates. The log of time under

observation (in days) will be the offset variable in the model. Categorical endpoints will be analyzed by logistic regression.

Safety endpoints will be summarized descriptively, providing detail of the frequency, type, severity and outcome of the events.

Other outcomes will be summarized descriptively.

CCI [redacted]

CCI [redacted]

8.6 Interim and Additional Planned Analyses

As the primary analysis is available after all subjects have completed the 6-month assessment, this analysis will be conducted at this stage. The full dataset up to and including the 6-month assessment will be subject to appropriate data cleaning for all variables involved in the primary analysis, consisting of post-entry validation checks and assessing the data for outliers, for example.

Interim analysis at this stage will also consider descriptive summaries of other outcomes. Data cleaning will be undertaken on all data involved in interim reporting.

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 designate 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. 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 Investigator will revise the subject information sheet and any other written information to be provided to the subjects and submit them to the IRB 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.

After the end of the study, samples will be stored at a Sponsor's designated biorepository under the supervision of Sponsor.

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.

In cases where the Investigator is not available, the Sponsor provides the appropriate means to contact a Sponsor physician. This includes the provision of a 24-hour contact number at a call center, whereby the health care providers will be given access to the appropriate Sponsor physician to assist with the medical emergency and to provide support for the management of the subject concerned.

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 (for example, IMP Dossier, Subject Information and ICF, as per national and local regulations) 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 at (Sponsor or designated organization).

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, IMP 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 Manual of Operations for eCRF handling guidelines.

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.

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 computed tomography (CT) or MRI scan images, ECG recordings, 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 Monitor performs source data verification. Printouts must be signed and dated by the Investigator, countersigned by the Monitor 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 calls and 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 (nonsubstantial) 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.

11 References Cited in the Text

Benedict RHB, DeLuca J, Phillips G, LaRocca N, Hudson LD, Rudick R. Validity of the Symbol Digit Modalities Test as a cognition performance outcome measure for multiple sclerosis. Mult Scler 2017;23(5):721–33.

Comi G, Cook SD, Giovannoni G, Rammohan K, Rieckmann P, Sørensen PS, Vermersch P, Hamlett AC, Viglietta V, Greenberg SJ. MRI outcomes with cladribine tablets for multiple sclerosis in the CLARITY study. J Neurol 2013;260:1136–46.

Cook S, Comi G, Rieckmann P, Rammohan K, Sørensen PS, Vermersch P, Martin E, Dangond F, Giovannoni G. Safety and Tolerability of Cladribine Tablets in Patients with Relapsing-Remitting Multiple Sclerosis (RRMS): Final Results from the 120-Week Phase IIIb Extension Trial to the CLARITY Study (P3.095). Neurology Apr 2016, 86 (16 Supplement) P3.095.

De Stefano N, Curtin F, Stubinski B, Blevins G, Drulovic J, Issard D, Shotekov P, Gasperini C. Rapid benefits of a new formulation of subcutaneous interferon beta-1a in relapsing-remitting multiple sclerosis. Mult Scler 2010;16(7):888-92.

Dubey D, Cano CA, Stuve O. Intractable and highly active relapsing multiple sclerosis – role of alemtuzumab. Neuropsychiatr Dis Treat 2015;11:2405–14.

EMA/424715/2017. PRAC confirms restrictions on the use of linear gadolinium agents Benefit-risk balance of certain linear gadolinium agents no longer favourable. 7 July 2017.

Fazekas F, Bajenaru O, Berger T, Fabjan TH, Ledinek AH, Jakab G, Komoly S, Kobys T, Kraus J, Kurča E, Kyriakides T, Lisý L, Milanov I, Nehrych T, Moskovko S, Panayiotou P, Jazbec SŠ, Sokolova L, Taláb R, Traykov L, Turčáni P, Vass K, Vella N, Voloshyná N, Havrdová E. How does fingolimod (gilenya(®)) fit in the treatment algorithm for highly active relapsing-remitting multiple sclerosis? Front Neurol 2013;4:10.

Feys P, Lamers I, Francis G, Benedict R, Phillips G, LaRocca N, Hudson LD, Rudick R. The Nine-Hole Peg Test as a manual dexterity performance measure for multiple sclerosis. Mult Scler 2017; 23(5):711–20.

Gibbons RD, Hedeker D, Dutoit S. Advances in analysis of longitudinal data. Annu Rev Clin Psychol, v. 6, p. 79-107, 2010. ISSN 1548-5951 (Electronic) 1548-5943 (Linking). Disponível em: < https://www.ncbi.nlm.nih.gov/pubmed/20192796 >.

Giovannoni G, Comi G, Cook S, Rammohan K, Rieckmann P, Soelberg Sørensen P, Vermersch P, Chang P, Hamlett A, Musch B, Greenberg SJ. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. N Engl J Med 2010;362(5):416-26.

Giovannoni G, Cook S, Rammohan K, Rieckmann P, Sørensen PS, Vermersch P, Hamlett A, Viglietta V, Greenberg S. Sustained disease-activity-free status in patients with relapsing-

remitting multiple sclerosis treated with cladribine tablets in the CLARITY study: a post-hoc and subgroup analysis. Lancet Neurol 2011;10(4):329-37.

Giovannoni G, Soelberg Sorensen P, Cook S, Rammohan K, Rieckmann P, Comi G, Dangond F, Adeniji AK, Vermersch P. Safety and efficacy of cladribine tablets in patients with relapsing-remitting multiple sclerosis: Results from the randomized extension trial of the CLARITY study. Mult Scler. 2018 Oct;24(12):1594-1604. doi: 10.1177/1352458517727603. Epub 2017 Sep 5.

Hirst CL, Pace A, Pickersgill TP, Jones R, McLean BN, Zajicek JP, Scolding NJ, Robertson NP. Campath 1-H treatment in patients with aggressive relapsing remitting multiple sclerosis. J Neurol. 2008 Feb;255(2):231-8. doi: 10.1007/s00415-008-0696-y. Epub 2008 Feb 20.

Kappos L, Antel J, Comi G, Montalban X, O'Connor P, Polman CH, Haas T, Korn AA, Karlsson G, Radue EW. Oral fingolimod (FTY720) for relapsing multiple sclerosis. N Engl J Med 2006;355(11):1124-40.

Leist TP, Comi G, Cree BA, Coyle PK, Freedman MS, Hartung HP, Vermersch P, Casset-Semanaz F, Scaramozza M. Effect of oral cladribine on time to conversion to clinically definite multiple sclerosis in patients with a first demyelinating event (ORACLE MS): a phase 3 randomised trial. Lancet Neurol 2014;13(3):257-67.

Leist TP, Weissert R. Cladribine: mode of action and implications for treatment of multiple sclerosis. Clin Neuropharmacol 2011;34(1):28-35.

Miller DH, Khan OA, Sheremata WA, Blumhardt LD, Rice GP, Libonati MA, Willmer-Hulme AJ, Dalton CM, Miszkiel KA, O'Connor PW. A controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2003;348(1):15-23.

Motl RW, Cohen JA, Benedict R, Phillips G, LaRocca N, Hudson LD, Rudick R. Validity of the timed 25-foot walk as an ambulatory performance outcome measure for multiple sclerosis. Mult Scler 2017;23(5):704–10.

Oreja-Guevara C. Overview of magnetic resonance imaging for management of relapsing-remitting multiple sclerosis in everyday practice. Eur J Neurol 2015;22 Suppl 2:22-7

Przybek J, Gniatkowska I, Mirowska-Guzel D, Członkowska A. Evolution of diagnostic criteria for multiple sclerosis. Neurol Neurochir Pol 2015;49(5):313-21.

Roar M, Illes Z, Sejbaek T. Practice effect in Symbol Digit Modalities Test in multiple sclerosis patients treated with natalizumab. Mult Scler Relat Disord 2016;10:116-122.

Rovira A, Auger C. Role of Contrast-enhanced Magnetic Resonance Imaging in Multiple Sclerosis. Eur Neurol Rev 2012;7(3):181-8.

Sormani MP, Arnold DL, De Stefano N. Treatment effect on brain atrophy correlates with treatment effect on disability in multiple sclerosis. Ann Neurol 2014;75(1):43-9

Tramacere I, Del Giovane C, Salanti G, D'Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev 2015;(9):CD011381.

Wattjes MP, Rovira À, Miller D, Yousry TA, Sormani MP, de Stefano MP, Tintoré M, Auger C, Tur C, Filippi M, Rocca MA, Fazekas F, Kappos L, Polman C, Barkhof F, Montalban X. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-establishing disease prognosis and monitoring patients. Nat Rev Neurol 2015;11(10):597-606.

12 Appendices

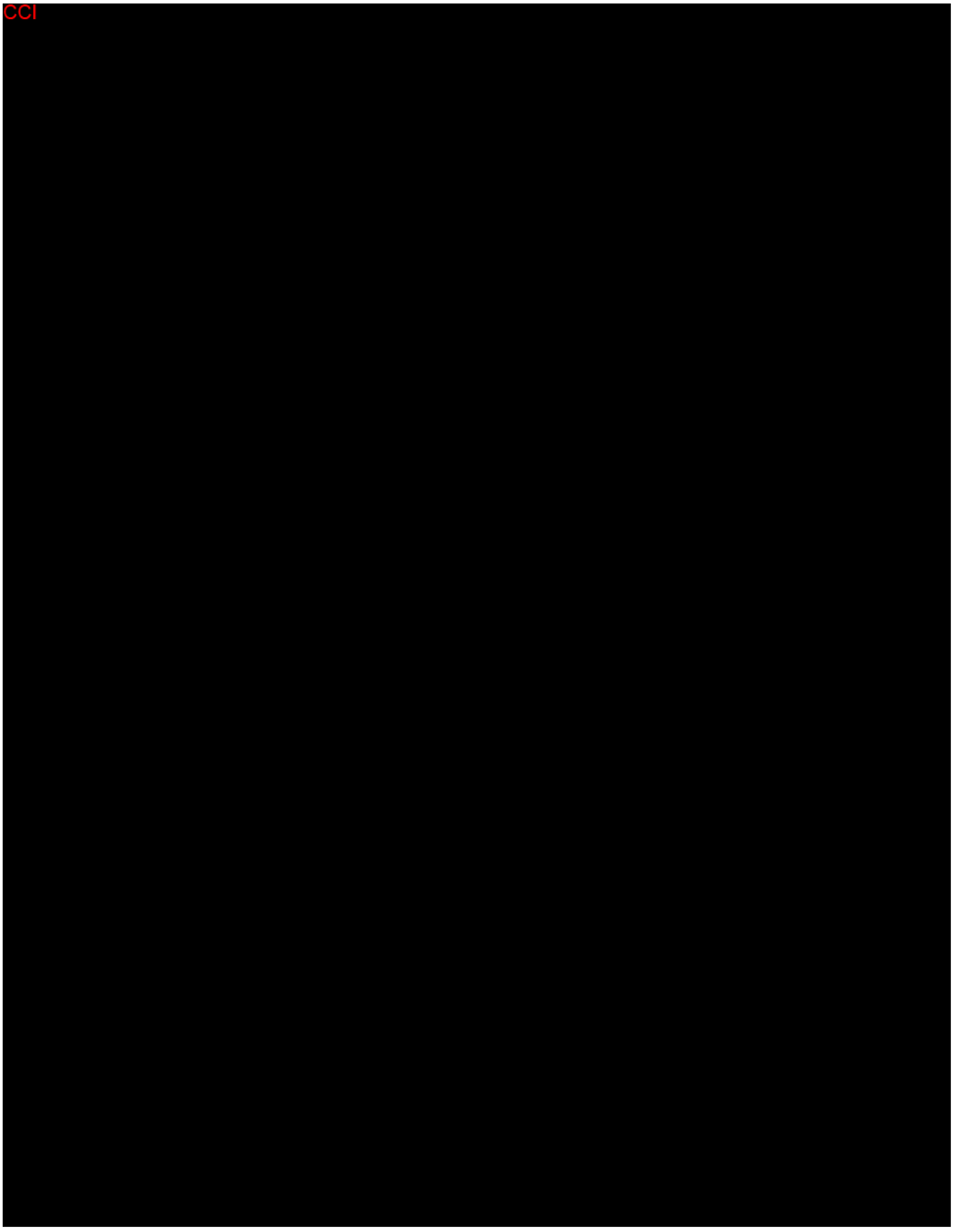
12.1 Appendix 1: Schedule of Assessments

Assessments	Pre-baseline Screening	Baseline	Month 1	Month 2	Month 3	Month 6	Month 12	Month 14	Month 15	Month 18	Early termination/ Month 24
Visit windows	Up to -3 months	+7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days	±7 days
Informed consent[1]	X										
Demographics, medical history	X										
Inclusion/exclusion criteria	X	X									
Weight[2]/ Cladribine Tablets dispensed		X	X				X				
IRT contacted	X	X	X				X				
Trial medication administered at site		X	X				X				
Physical examination[3]	X	X				X	X			X	X
Lymphocyte count[4]	X			X		X	X	X		X	X
Serology[5]	X						X				
TB (active, latent)[6]	X						X				
Urine pregnancy test[7]	X	X					X				
MRI	X	X	X	X	X	X	X		X	X	X
CCI [redacted]											
Disability (EDSS/KFS)	X	X				X	X			X	X
Disability (9HPT)	X	X				X	X			X	X
Disability (T25FW)	X	X				X	X			X	X
Cognition (SDMT)		X				X	X			X	X
Relapse count[9]		X					X				X
Adverse events, concomitant medications and procedures[10]	X	X	X	X	X	X	X	X	X	X	X
Collection and review of subject diary[10]		X	X	X	X	X	X	X	X	X	X

Abbreviations: 9HPT=9-Hole Peg Test; EDSS=Expanded Disability Status Scale; KFS= Kurtzke Functional System; IRT=interactive response technology; MRI=magnetic resonance imaging; SDMT=Symbol Digit Modalities Test; T25FW=Timed 25-Foot Walk; TB=tuberculosis

1. Informed Consent should be obtained prior to any trial-specific assessments are undertaken
2. Weight to be measured before each treatment course for calculating appropriate dose of cladribine
3. Includes vital signs (blood pressure, heart rate, body temperature)

4. To be done at a local laboratory. If the lymphocyte count at screening is done before 4 weeks from Baseline, it should be repeated within 4 weeks of Baseline. 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
5. To be done at a local laboratory. Serology test for HIV, Hepatitis C, Hepatitis B to be done at screening and at month 12, and varicella to be done at screening. Subjects with a negative varicella serology will be included after 4 to 6 weeks of receipt of varicella vaccination.
6. Screening test for active and latent TB will be done as per local guideline (to be done at a local laboratory)
7. To be done at a local laboratory. As per local guideline, urine or serum pregnancy test may be done
8. CCI [redacted]
9. Captured in subject diary when at home
10. May be captured by the trial site personnel and/or trial nurse into eCRF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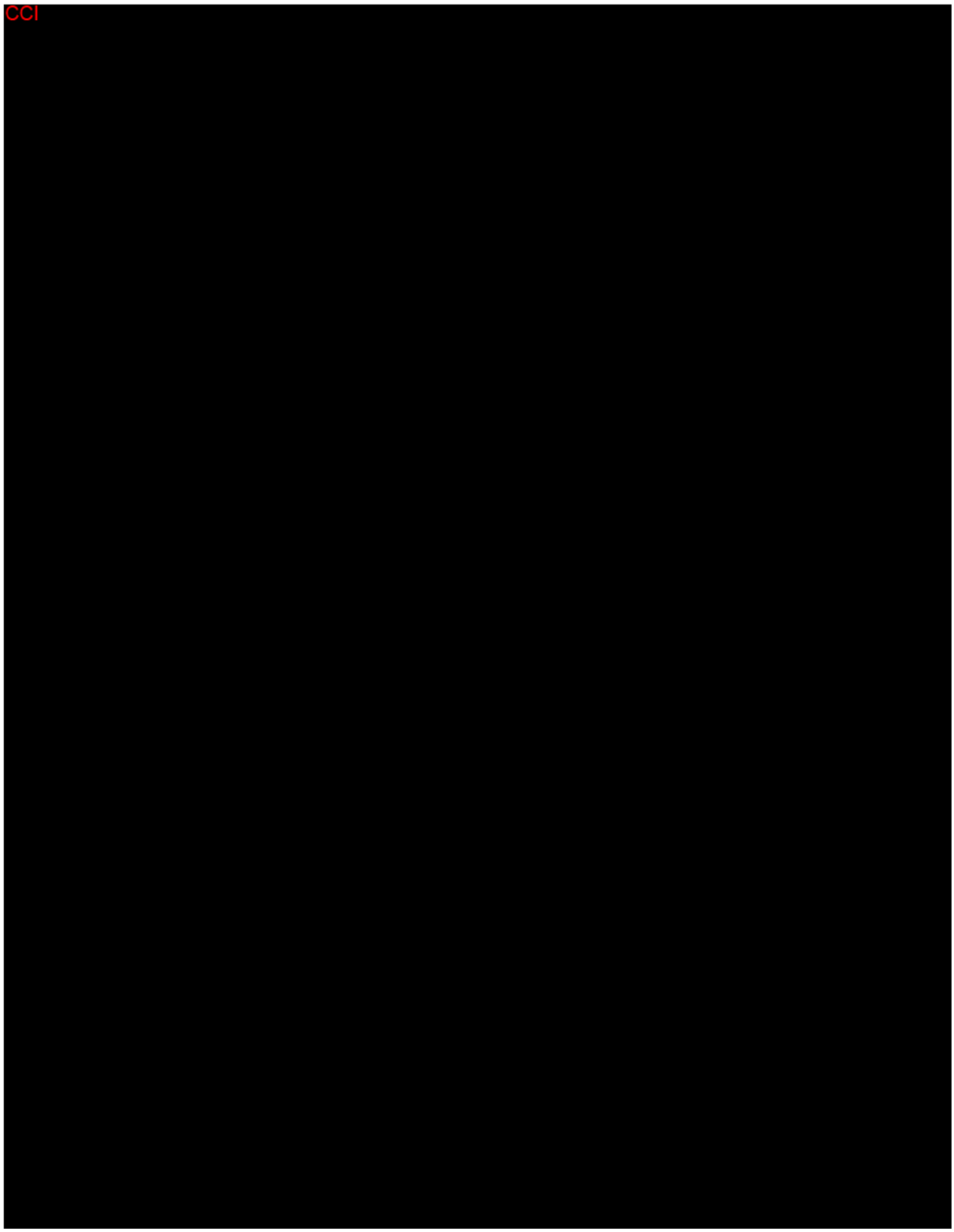
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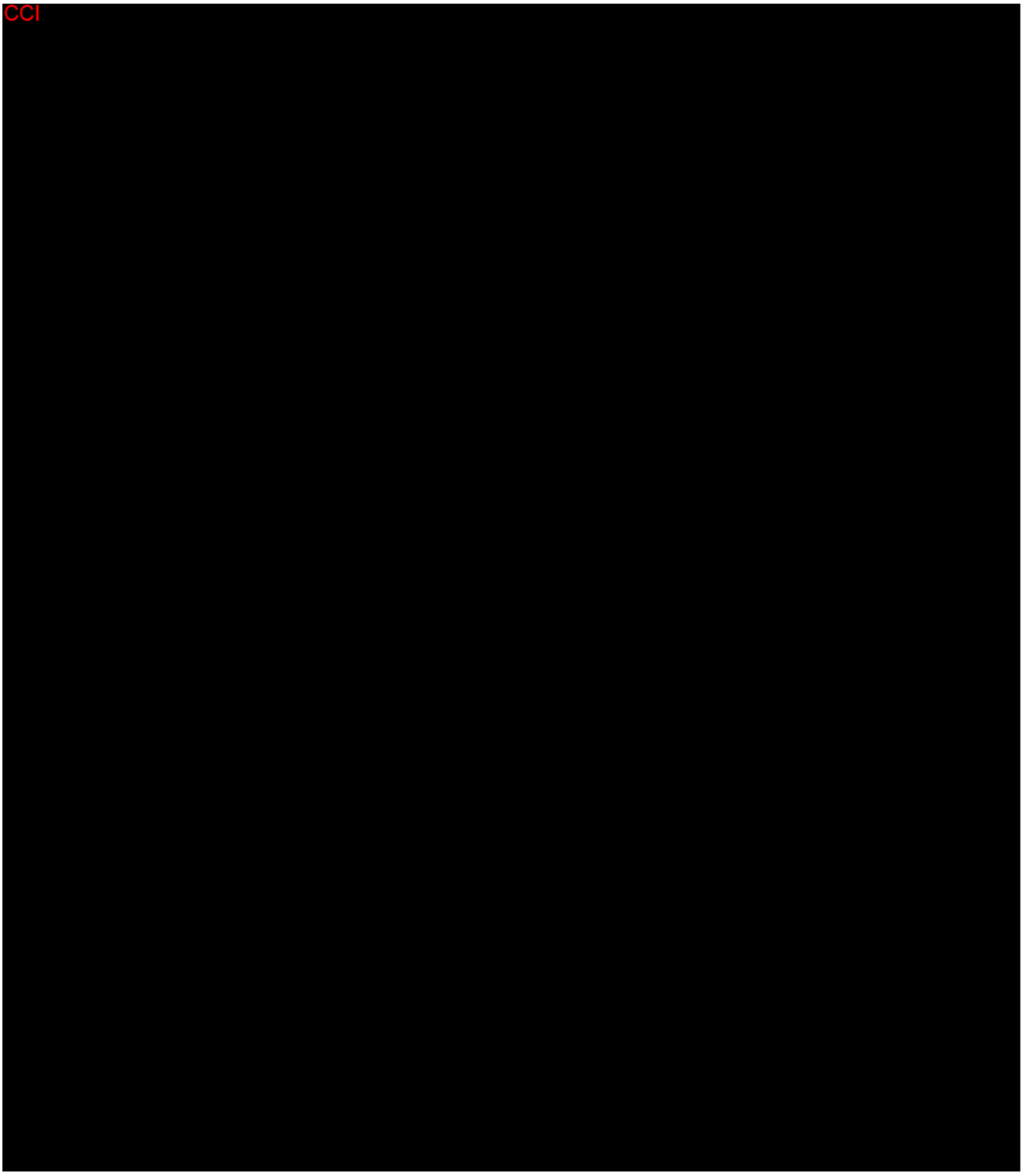
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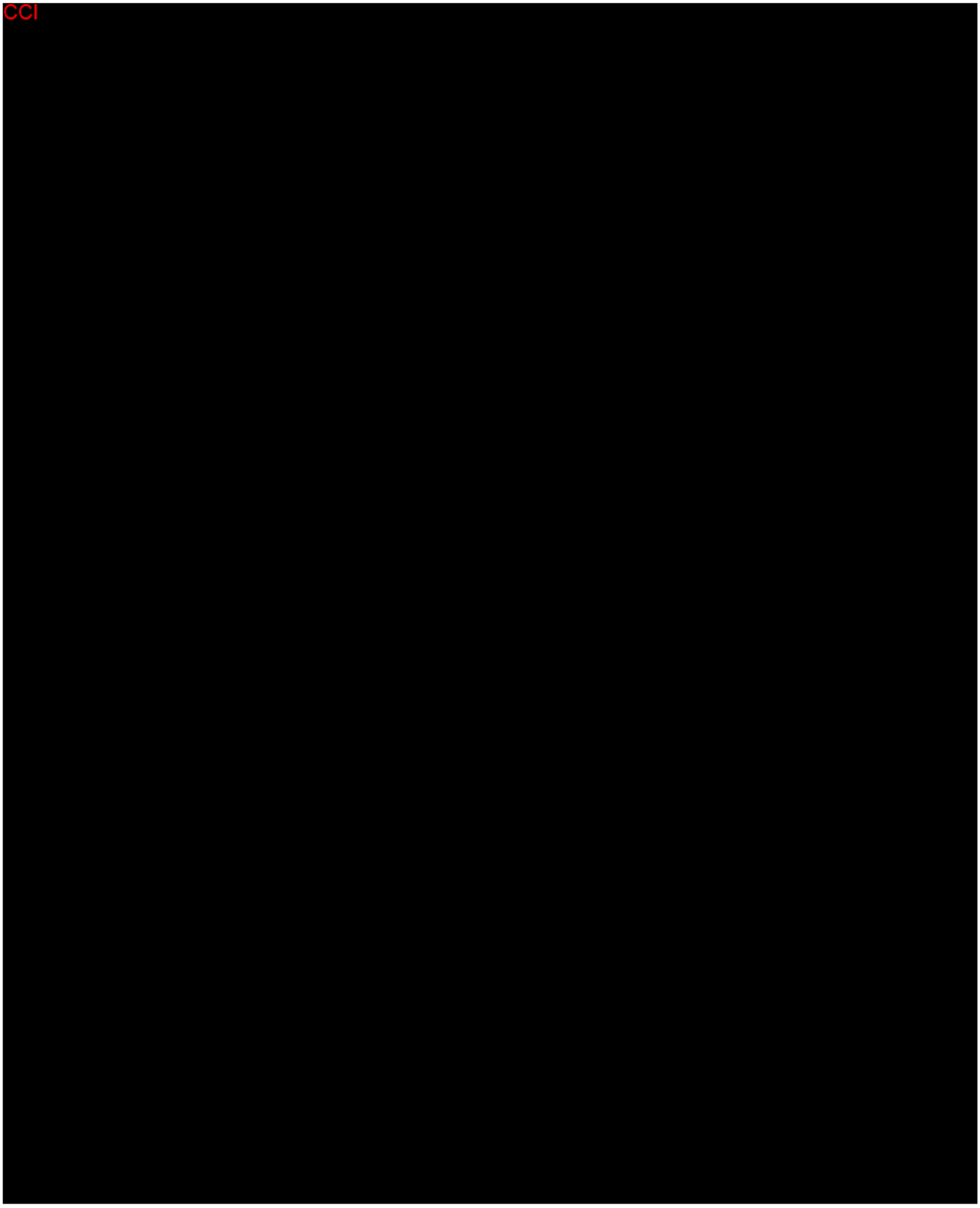

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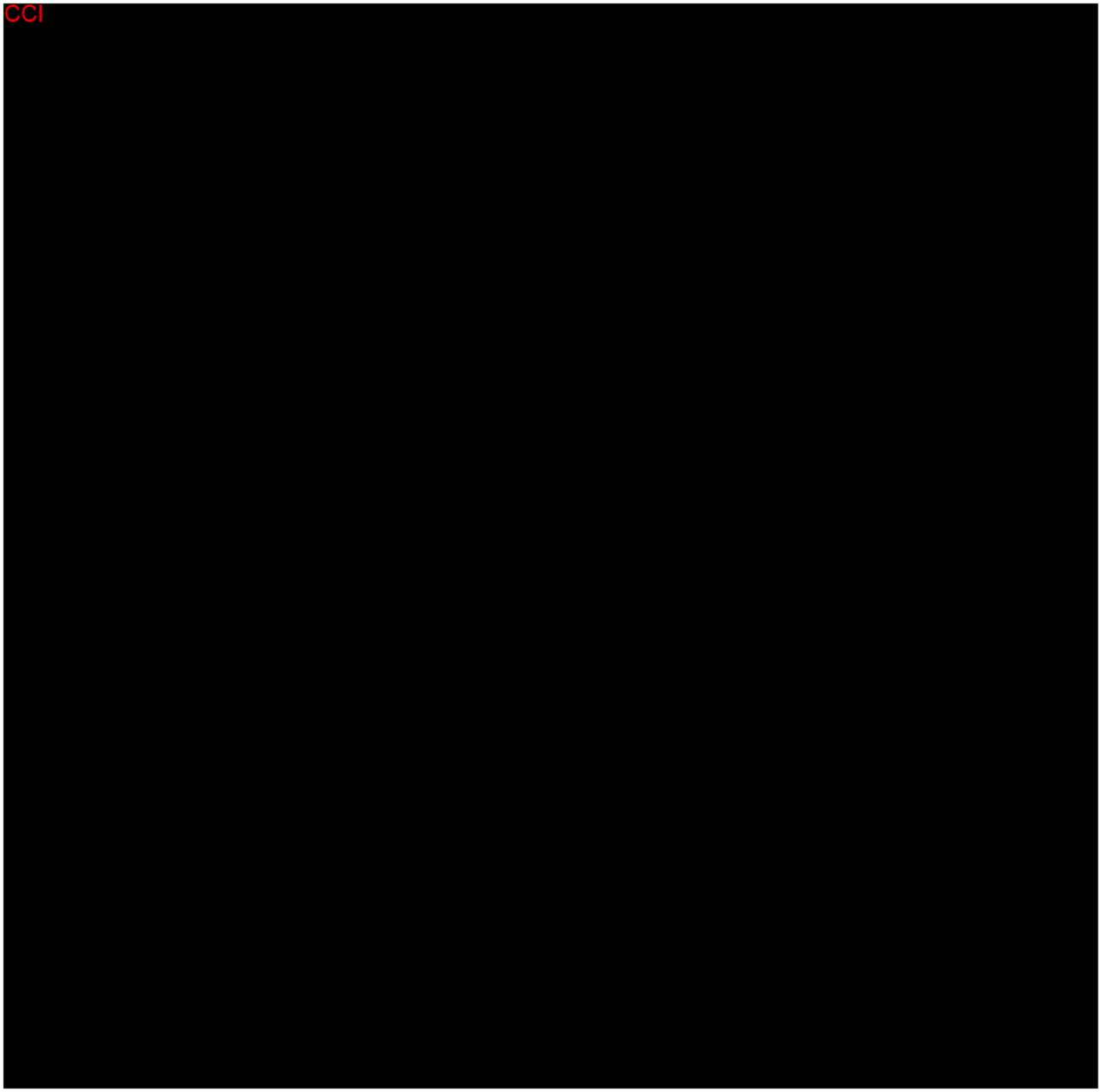
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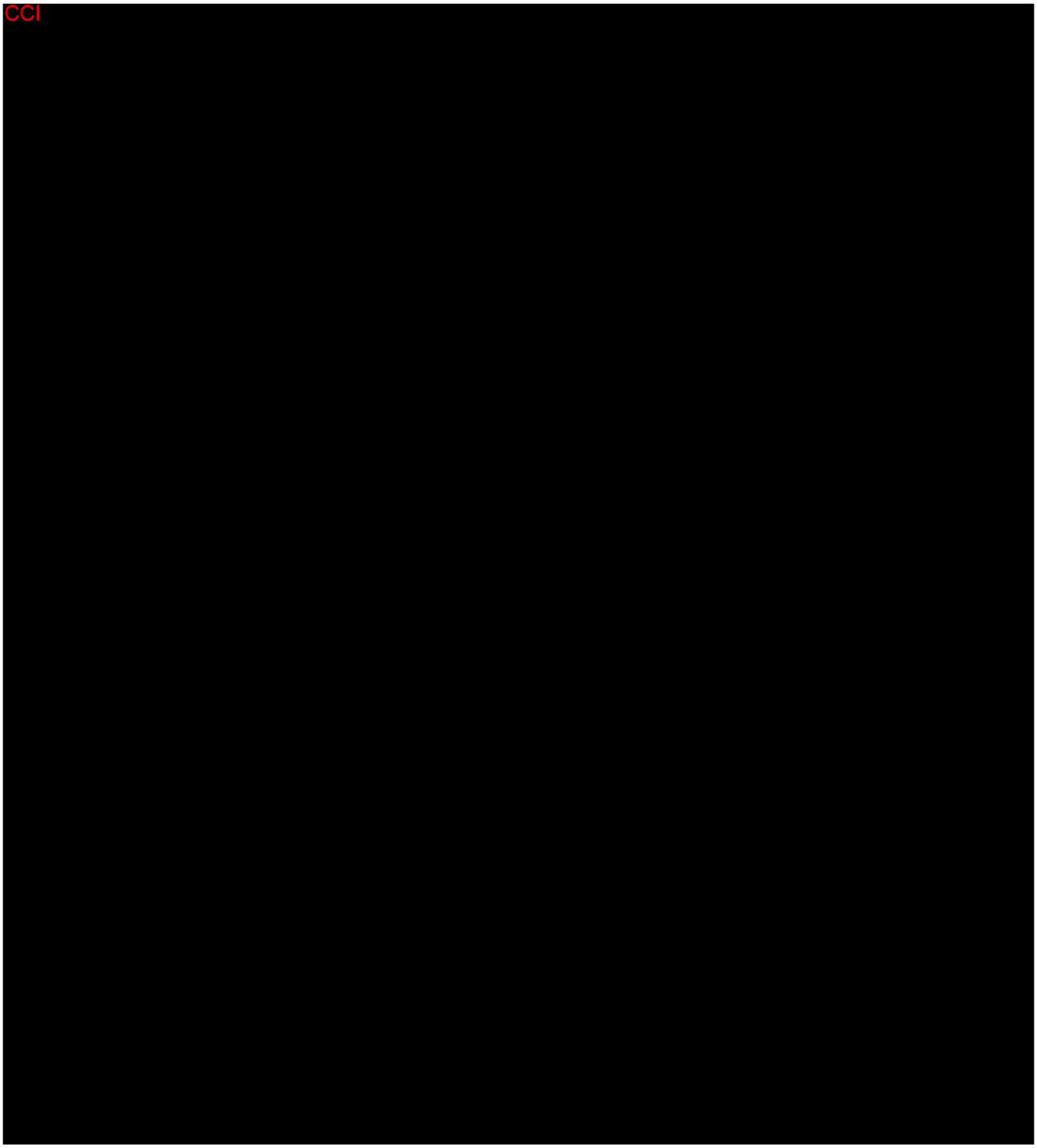

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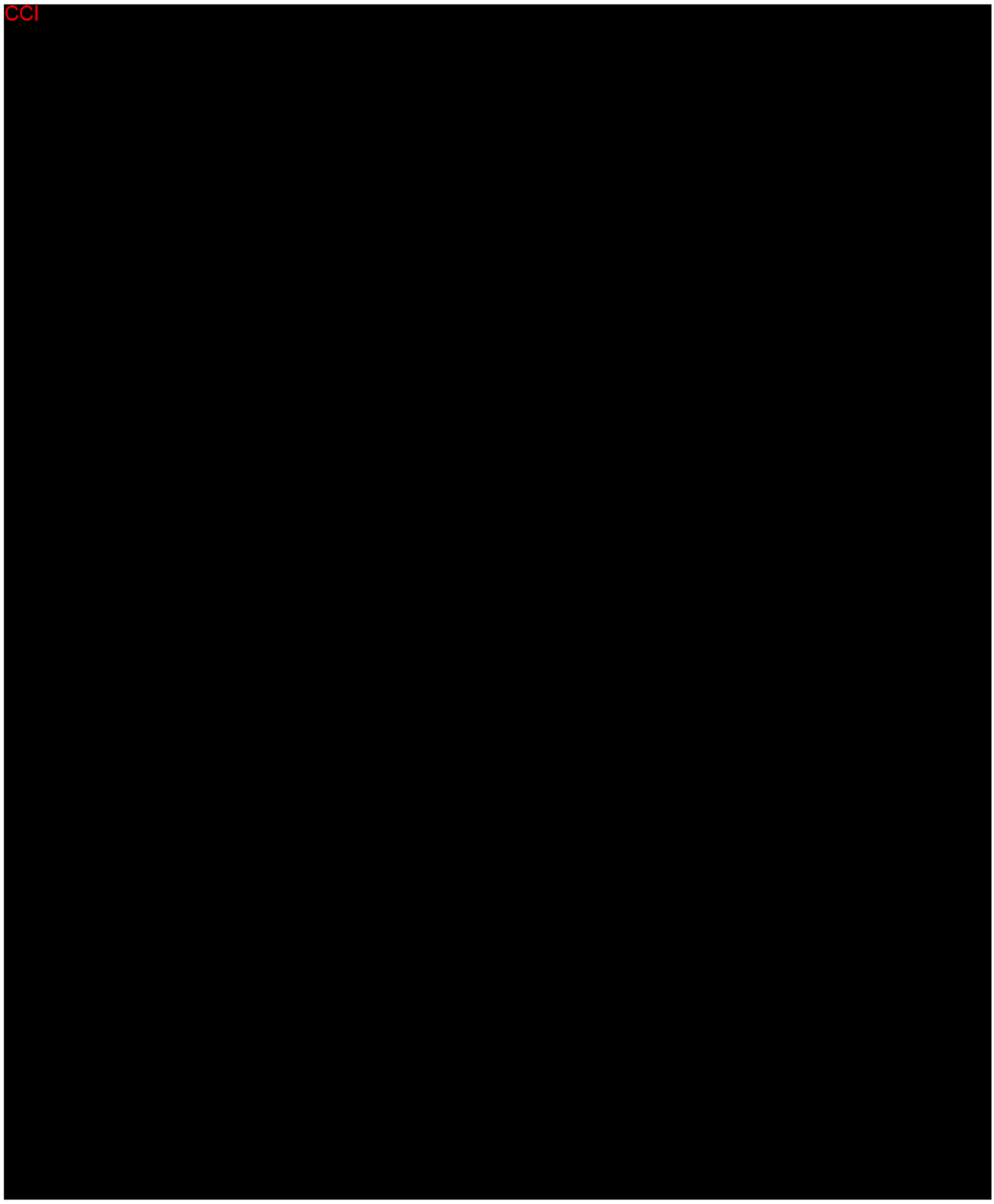
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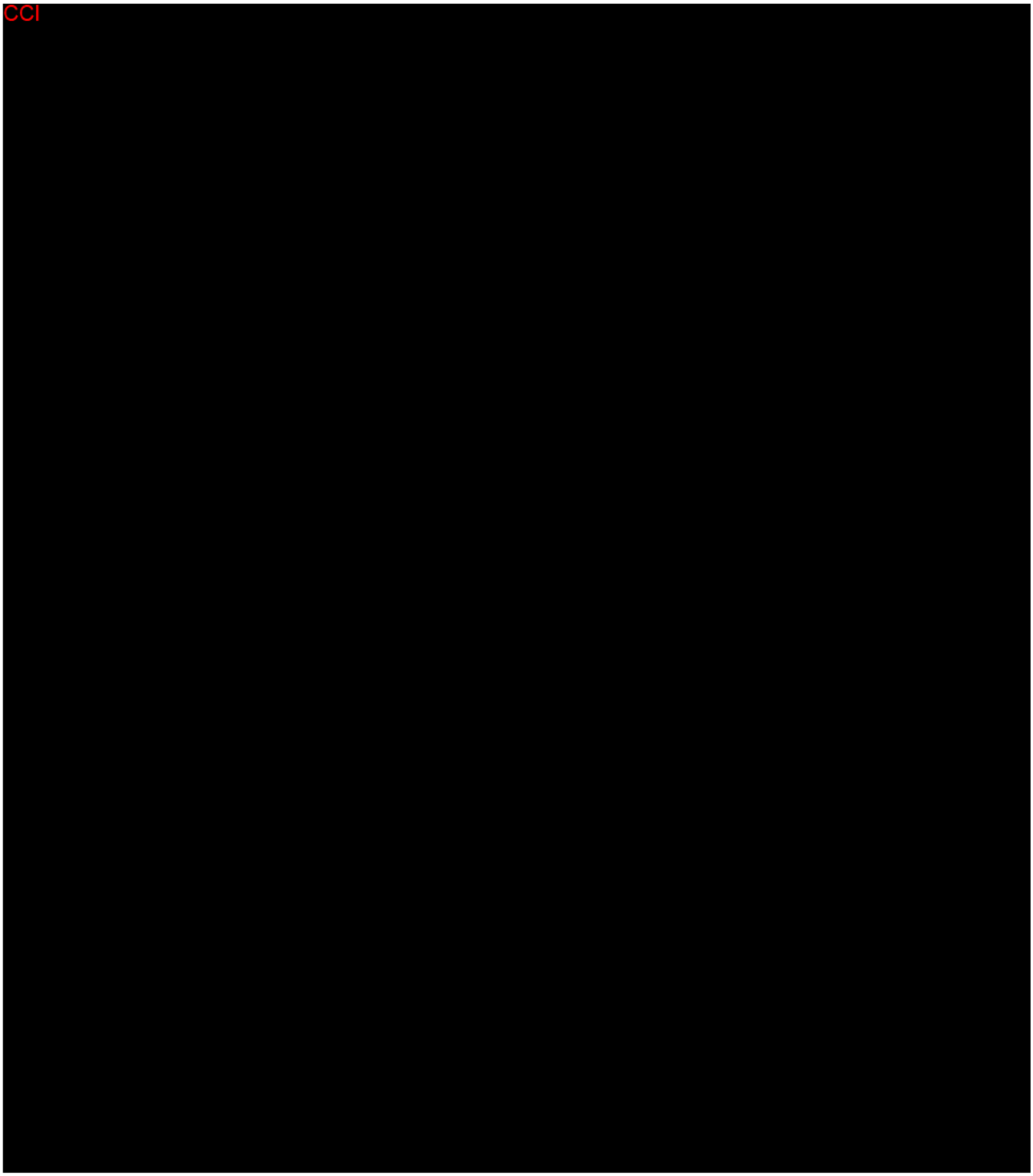
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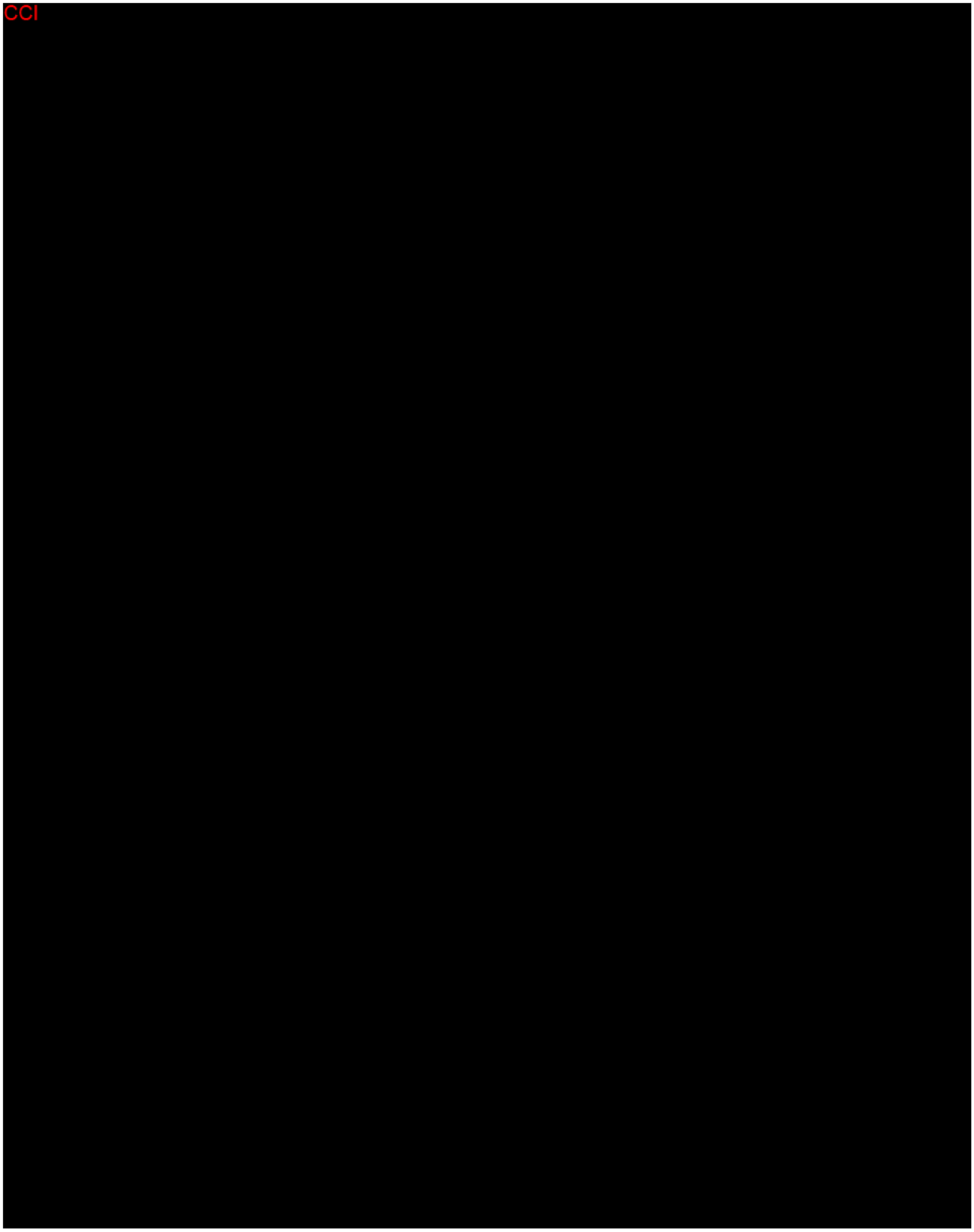
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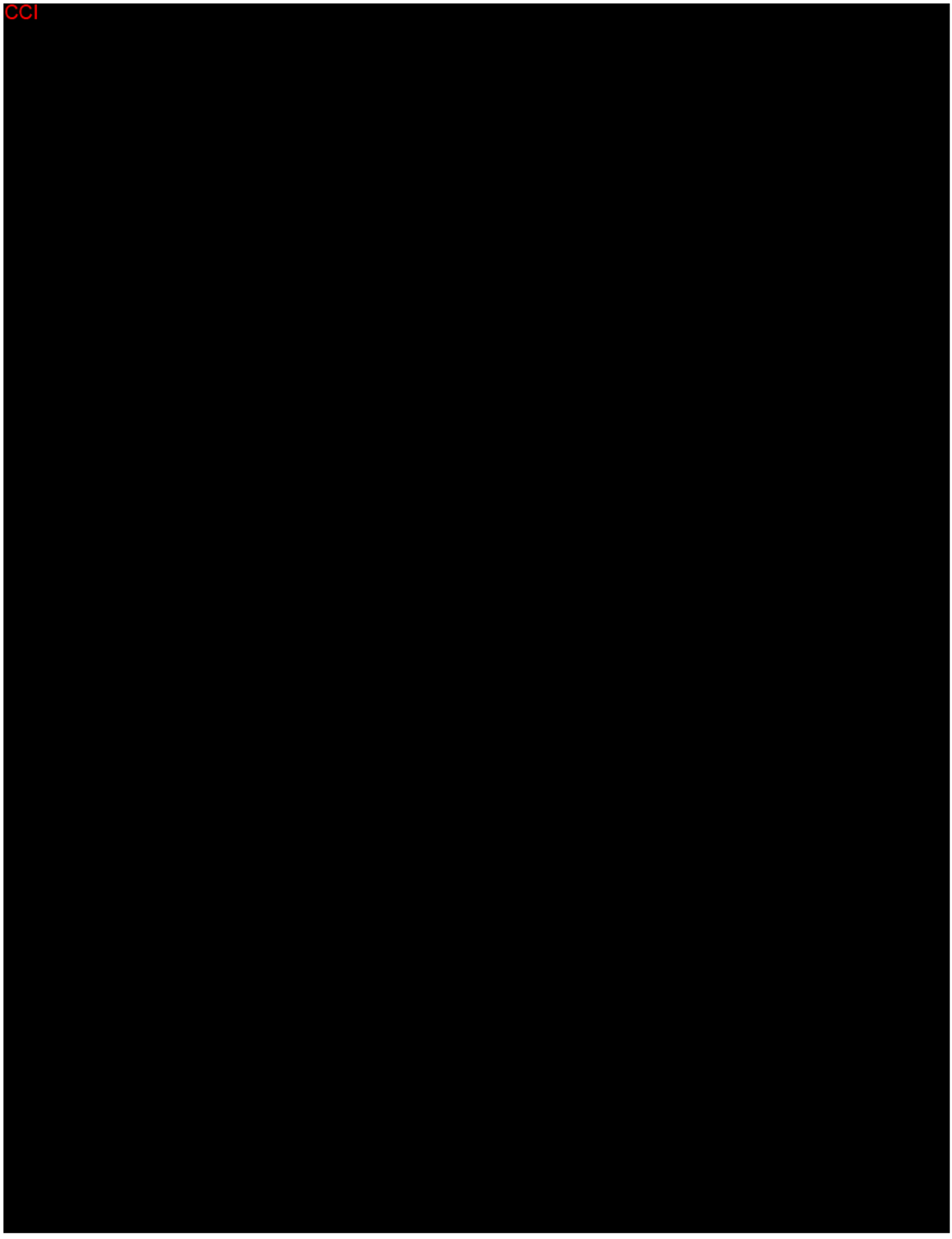
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12.6 Appendix 6: 9-Hole Peg Test (9HPT)

General Information:

- The 9HPT should be conducted with the dominant arm first
- One practice trial (per arm) should be provided prior to timing the test
- Timing should be performed with a stopwatch and recorded in seconds
- The stop watch is started when the patient touches the first peg
- The stop watch is stopped when the patient places the last peg in the container

Set-up (Mathiowetz et al, 1985):

- A square board with 9 holes,
    - holes are spaced 3.2 cm (1.25 inches) apart
    - each hole is 1.3 cm (0.5 inches) deep
- 9 wooden pegs should be .64 cm (.25 inches) in diameter and 3.2 cm (1.25 inches) long
- A container that is constructed from .7 cm (.25 inches) of plywood, sides are attached (13 cm x 13 cm) using nails and glue
- The peg board should have a mechanism to decrease slippage. Self-adhesive bathtub appliqués were used in the trial
- The pegboard should be placed in front of the patient, with the container holding the pegs on the side of the dominant hand

Patient Instructions (Mathiowetz et al, 1985):

- The instructions should be provided while the activity is demonstrated
- The patient's dominant arm is tested first
- Instruct the patient to:
    - "Pick up the pegs one at a time, using your right (or left) hand only and put them into the holes in any order until the holes are all filled. Then remove the pegs one at a time and return them to the container. Stabilize the peg board with your left (or right) hand. This is a practice test. See how fast you can put all the pegs in and take them out again. Are you ready? Go!"

- After the patient performs the practice trial, instruct the patient:
    - "This will be the actual test. The instructions are the same. Work as quickly as you can. Are you ready? Go!" (Start the stop watch when the patient touches the first peg.)
    - While the patient is performing the test say "Faster"
    - When the patient places the last peg on the board, instruct the patient "Out again…faster."
    - Stop the stop watch when the last peg hits the container.
- Place the container on the opposite side of the pegboard and repeat the instructions with the non-dominant hand.

Dominant Hand (circle one): Right Left Time to complete the test in seconds:

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

Date: _____ Dominant Hand: _____ Non-Dominant Hand: _____

References: Mathiowetz V, Weber K, Kashman N, Volland G. Adult Norms for the Nine Hole Peg Test of Finger Dexterity. The Occupational Therapy Journal of Research. 1985;5:24- 33.

12.7 Appendix 7: Kurtzke Functional System

Pyramidal Function

0. Normal
1. Abnormal signs without disability
2. Minimal disability
3. Mild or moderate paraparesis or hemiparesis (detectable weakness but most function sustained for short periods, fatigue a problem); severe monoparesis (almost no function)
4. Marked paraparesis or hemiparesis (function is difficult); moderate quadriparesis (function is decreased but can be sustained for short periods); or monoplegia
5. Paraplegia, hemiplegia or marked quadriparesis
6. Quadriplegia
9. Unknown

Cerebellar Function

0. Normal
1. Abnormal signs without disability
2. Mild ataxia (tremor or clumsy movements easily seen, minor interference with function)
3. Moderate truncal or limb ataxia (tremor or clumsy movements interfere with function in all spheres)
4. Severe ataxia in all limbs (most function is very difficult)
5. Unable to perform co-ordinated movements due to ataxia
9. Unknown

Record #1 in small box when weakness (grade 3 or worse on pyramidal) interferes with testing.

Brain Stem Function

0. Normal
1. Signs only
2. Moderate nystagmus or other mild disability
3. Severe nystagmus, marked extraocular weakness or moderate disability of other cranial nerves
4. Marked dysarthria or other marked disability
5. Inability to swallow or speak
9. Unknown

Sensory Function

0. Normal
1. Vibration or figure-writing decrease, only in one or two limbs
2. Mild decrease in touch or pain or position sense, and/or moderate decrease in vibration in one or two limbs; or vibratory decrease alone in three or four limbs
3. Moderate decrease in touch or pain or position sense, and/or essentially lost vibration in one or two limbs; or mild decrease in touch or pain and/or moderate decrease in all proprioceptive tests in three or four limbs

4. Marked decrease in touch or pain or loss of proprioception, alone or combined, in one or two limbs; or moderate decrease in touch or pain and/or severe proprioceptive decrease in more than two limbs
5. Loss (essentially) of sensation in one or two limbs; or moderate decrease in touch or pain and/or loss of proprioception for most of the body below the head
6. Sensation essentially lost below the head
9. Unknown

Bowel and Bladder Function
(Rate on the basis of the worse function, either bowel or bladder)

0. Normal
1. Mild urinary hesitancy, urgency or retention
2. Moderate hesitancy, urgency, retention of bowel or bladder, or rare urinary incontinence (intermittent self-catheterization, manual compression to evacuate bladder or finger evacuation of
stool)
3. Frequent urinary incontinence
4. In need of regular intermittent catheterization (and constant use of measures to evacuate stool)
5. Indwelling catheter
6. Loss of bowel and bladder function
9. Unknown

Visual (or Optic) Function

0. Normal
1. Scotoma with visual acuity (corrected) better than 6/9
2. Worse eye with maximal visual acuity (corrected) of 6/9 to 6/12
3. Worse eye with maximal visual acuity (corrected) of 6/18-6/24
4. Worse eye with maximal visual acuity (corrected) of 6/36-6/60 or Grade 3 plus maximal acuity of better eye of 6/18 or less
5. Worse eye with maximal visual acuity (corrected) less than 6/60 or Grade 4 plus maximal acuity of better eye of 6/18 or less
6. Grade 5 plus maximal visual acuity of better eye of 6/18 or less
9. Unknown

Cerebral (or Mental) Function

0. Normal
1. Mood alteration only (Does not affect EDSS score)
2. Mild decrease in mentation
3. Moderate decrease in mentation
4. Marked decrease in mentation (chronic brain syndrome - moderate)
5. Dementia or chronic brain syndrome - severe or incompetent
9. Unknown

Sources: Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). Neurology. 1983 Nov;33(11):1444-52

Guidelines for KFS

Pyramidal Function

Test shoulder abduction, finger extension, finger abduction, hip flexion, ankle dorsiflexion

Score:

Mild:	4/5
Moderate:	3/5 (implies full range of movement vs. gravity)
Severe:	any muscle group is 2/5 or less

Paraplegia means 0-1/5 in all lower limb muscle groups

Cerebellar Function

Test finger-nose test, rapid alternating movements, heel-knee-shin test, gait

Score limb ataxia

Mild:	abnormality on finger-nose test or rapid alternating movements, not both
Moderate:	both finger-nose and rapid alternating movements abnormal, still able to hit target
Severe:	marked intention tremor, unable to hit target

Brain Stem Function

Moderate nystagmus:	sustained nystagmus on 30° lateral gaze but not in primary position
Mild disability:	clinically detectable numbness, facial weakness, dysarthria or other cranial nerve deficit of which the subject is aware
Severe nystagmus:	nystagmus in primary position and/or oscillopsia and/or internuclear ophthalmoplegia with nystagmus of abducting eye
Moderate disability:	diplopia without complete paralysis of any eye movement, analgesia without anaesthesia in trigeminal territory, weakness of eye closure and angle of mouth or obvious dysarthria during ordinary conversation not impairing comprehensibility
Severe/marked dysarthria:	dysarthria impairing comprehensibility
Severe/marked disability:	complete loss of movement of either eye in one direction, complete loss of sensation in the whole territory of one division of either trigeminal nerve, unilateral facial palsy, any difficulty with swallowing

Sensory Function

Ask if subject has numbness or loss of sensation
Test vibration with 128 Hz tuning fork on index and hallux tips
If report of numbness or vibration sensation abnormal:
Test pinprick pain and light touch on dorsum of index and hallux distal phalanx
Test position sense at DIP joint of index and hallux

If abnormal:	test each modality at wrist, elbow, ankle, and knee
Mild:	diminished but not absent at index or hallux only
Moderate:	absent at index, or hallux only
Marked/severe:	absent up to and including wrist or ankle only

Bowel and Bladder Function

Mild:	does not affect life style
Moderate:	has to wear pads or alter life-style to be near lavatory. Rare incontinence means not more than once in the last week. Intermittent catheterization less than once a day.
Severe:	Frequent urinary incontinence at least once a day during the last week or intermittent catheterization once
Severe:	Requires intermittent catheterization more than once a day.

Visual (or Optic) Function

Test best corrected vision: use a pinhole and Snellen test type.
Score acuity as smallest completely correct line.
To score 1, visual acuity will be 6/6 but subject reports monocular visual blurring and then describes a scotoma on Amsler chart or equivalent with either eye.

Cerebral (or Mental) Function

Mood alteration only:	subject complains of depression or is considered depressed by investigator or "significant other".
Mild decrease in mentation:	subject and "significant other" report impairment of memory or reasoning which does not alter life-style and is not apparent while taking the history or performing the routine neurological examination.
Moderate decrease in mentation:	interferes to some extent with life-style and evident on simple testing. Still oriented in time place and person.
Severe/marked decrease in mentation:	marked effect on life-style but still more or less orientated.
Dementia or chronic brain syndrome:	grossly demented and more or less completely disorientated in time, place and person.

12.8 Appendix 8: Expanded Disability Status Score (EDSS)

General

- The Evaluating Physician will complete the EDSS.
- The same individual should remain as the Evaluating Physician for each subject, except when exceptional circumstances make this impossible.
- Prior to each neurological assessment, the Evaluating Physician **should not** refer to any previous neurological assessments carried out on that subject.
- The current EDSS will be recorded (i.e., the EDSS as assessed during the visit).
- The EDSS obtained at screening and baseline visits must fall between *x-y* as defined by protocol inclusion criteria.

EDSS SCORING

- **0.0** Normal neurological exam [all grade 0 in all FS scores*]
- **1.0** No disability, minimal signs in one FS* (i.e., grade 1)
- **1.5** No disability, minimal signs in more than one FS* (more than 1 FS grade 1)
- **2.0** Minimal disability in one FS (one FS grade 2, others 0 or 1)
- **2.5** Minimal disability in 2 FS (2 FS grade 2, others 0 or 1)
- **3.0** Moderate disability in one FS (one FS grade 3, others 0 or 1) or mild disability in 3 or 4 FS (3 or 4 FS grade 2, others 0 or 1) though fully ambulatory
- **3.5** Fully ambulatory but with moderate disability in one FS (one grade 3) and one or 2 FS grade 2; or 2 FS grade 3 (others 0 or 1) or 5 grade 2 (others 0 or 1)
- **4.0** Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1), or combination of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 500 meters
- **4.5** Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability usually consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps; able to walk without aid or rest some 300 meters
- **5.0** Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (e.g., to work a full day without special provisions); (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combinations of lesser grades usually exceeding specifications for step 4.0)

- **5.5** Ambulatory without aid for about 100 meters; disability severe enough to preclude full daily activities; (Usual FS equivalents are one grade 5 alone, others 0 or 1; or combination of lesser grades usually exceeding those for step 4.0)
- **6.0** Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting; (Usual FS equivalents are combinations with more than 2 FS grade 3+)
- **6.5** Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting; (Usual FS equivalents are combinations with more than 2 FS grade 3+)
- **7.0** Unable to walk beyond approximately 5 meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day; (Usual FS equivalents are combinations with more than one FS grade 4+; very rarely pyramidal grade 5 alone)
- **7.5** Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair; (Usual FS equivalents are combinations with more than one FS grade 4+)
- **8.0** Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms; (Usual FS equivalents are combinations, generally grade 4+ in several systems)
- **8.5** Essentially restricted to bed much of day; has some effective use of arms(s); retains some self-care functions; (Usual FS equivalents are combinations, generally 4+ in several systems)
- **9.0** Helpless bed patient; can communicate and eat; (Usual FS equivalents are combinations, mostly grade 4+)
- **9.5** Totally helpless bed patient; unable to communicate effectively or eat/swallow; (Usual FS equivalents are combinations, mostly grade 4+)
- **10.0** Death due to MS

*Excludes cerebral function grade 1

Note 1: EDSS steps 1.0 to 4.5 refer to subjects who are fully ambulatory and the precise step number is defined by the FS score(s). EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation and usual equivalents in FS scores are provided.

Note 2: EDSS should not change by 1.0 step unless there is a change in the same direction of at least one step in at least one FS.

		Expanded Disability Status Score (EDSS)													
		0	**1**	**1.5**	**2**	**2.5**	**3**		**3.5**			**4**			
K	1	0	1	>1	n	n	n	n	n	n	n	n	n	n	n
F	2	0	0	0	1	2	0	3, 4	1, 2	0	5	0	6, 7	≥3	≥1

S	3	0	0	0	0	0	1	0	1	2	0	0	0	1	2
	4	0	0	0	0	0	0	0	0	0	0	1	0	0	0

n = 0 to 7 Functional Systems scored with this grade

Scores of 4.5 and above *are determined by ambulation distances as follows:*
4.0 *Able to walk at least 500 meters without aid*
4.5 *Able to walk 300-499 meters without aid*
5.0 *Able to walk 200-299 meters without aid*
5.5 *Able to walk 100-199 meters without aid*
6.0 *Able to walk 5-99 meters without aid or with unilateral assistance is able to walk at least 100 meters*
6.5 *Bilateral assistance required to walk but able to walk at least 20 meters; or unilateral assistance needed but able to walk between 5-99 meters*
7.0 *Only able to walk between 1- 5 meters even with assistance*
7.5 *Unable to walk more than a few steps (i.e., not able to walk at all or able to walk a maximum of about 1 meter)*
8.0-9.5 *Investigator judgment*

The guiding principle: if a patient fails to meet the criteria of a given level, they are automatically assigned to the next higher level. If a patient does not need aids to walk (i.e., walks unassisted) but can only walk 50 meters, they are to be considered EDSS 6.0 since they do not satisfy the criteria for EDSS 5.5.

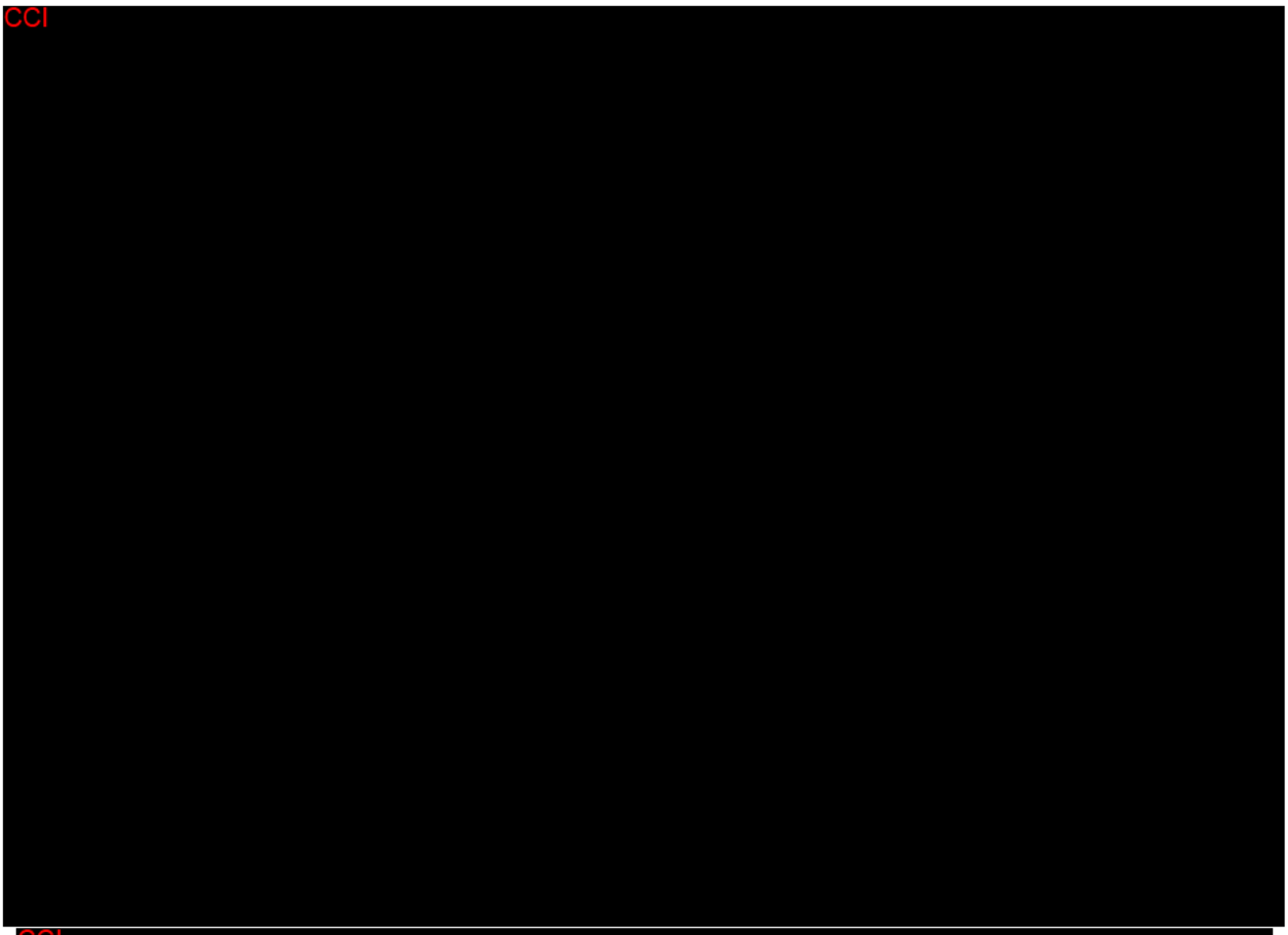
12.9 Appendix 9: Blood Volumes

Core trial (n=265 subjects)

CCI [redacted]				
Local laboratory analysis				
Lymphocyte count	1	7	Pre-Baseline, end of Months 2,6,12,14,18,24	7
Serology	3.5	2	Pre-Baseline and end of Month 12	7
TB (Quantiferon test)**	3	2		6
Varicella serology **	3	1	Pre-Baseline	3
Total	Maximum 25.5	-		108

*Baseline, and end of Month 3, 6, 12, 15, 18 and 24 for all above panel except NFL at Baseline, and end of Month 12 and 24 **In case, investigator decides to test for Latent TB by Quantiferon test or decides to test varicella serology if subject provide no prior history of varicella infection

CCI



CCI


CCI

12.10 Appendix 10: Example of Subject Diary

Subject Diary Card: Week ___ to ____

Patient Initials:	*Patient Number:*

Dear Subject,

Please complete this diary card (with a pen) for each daily dose of study drug and always take it with you to the hospital when you visit.

Please also remember to **bring your unused study drug** with you in their original containers. You will also need to **bring back the blister packs and boxes from your used study drug**.

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 study drug.

Start Date	Stop Date	List any new medications or changes in the medications	Specify reason for taking any specific concomitant medication. All medications, drug should be listed here e.g. OTC or painkillers… as well.

Subject Study Drug Medication Record

Week	Date	Time (circle am or pm)	Number of tablets taken	Kit #	Comments***
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			

Week	Date	Time (circle am or pm)	Number of tablets taken	Kit #	Comments***
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am pm			
		am			

Week	Date	Time (circle am or pm)	Number of tablets taken	Kit #	Comments***
		pm			
		am pm			
		am pm			
		am pm			

Comments *** If a tablet was missed, please record the date and reason for missed dose

SYMPTOMS RECORD		
Start Date	**Stop Date**	Briefly list any problem or discomfort you experienced (use as many lines as necessary)


CCI

CCI

[redacted]

12.12 Appendix 12: Birth control methods which may be considered as highly effective

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[1]:
  - oral
  - intravaginal
  - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation[1]:
  - oral
  - injectable
  - implantable[2]
- intrauterine device (IUD)[2]
- intrauterine hormone-releasing system (IUS)[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 Childbearing 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.

12.13 Appendix 13: Mavenclad 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 patient receives 10 mg or 20 mg (one or two tablets) as a single daily dose, depending on body weight. For details, see Tables 1 and 2 below.

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 cladribine in patients weighing less than 40 kg has not been investigated.

Table 1 Dose of MAVENCLAD per treatment week by patient weight in each treatment year

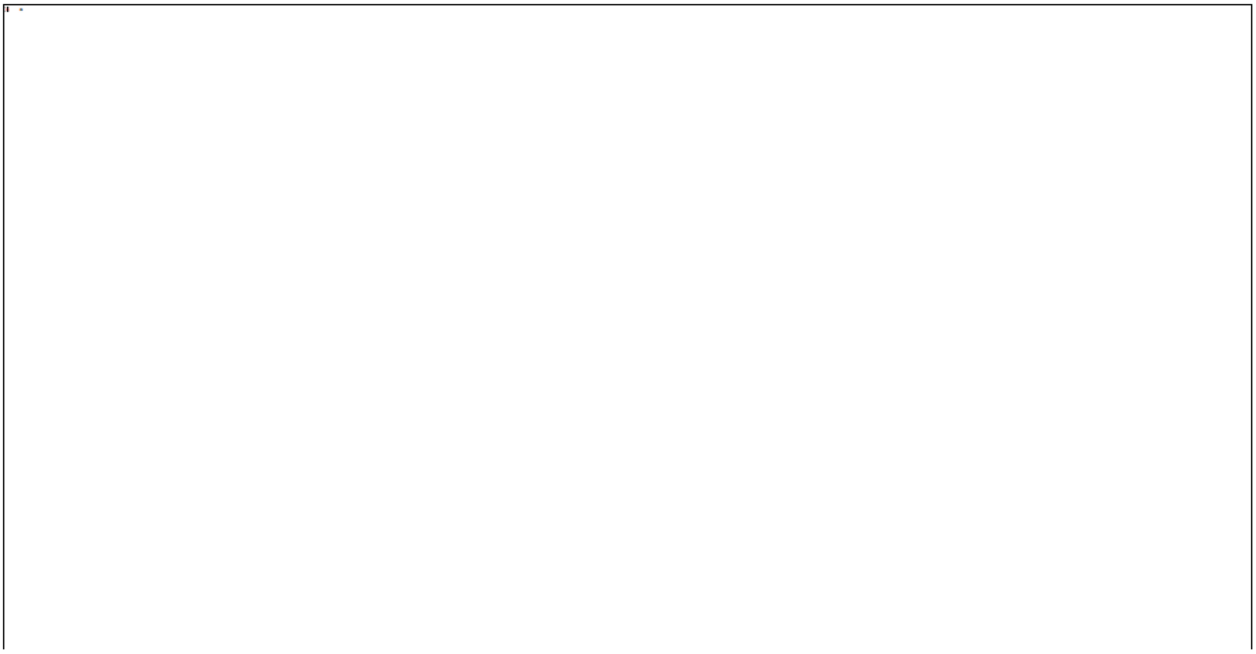
Weight range	Dose in mg (number of 10 mg tablets) per treatment week	
kg	Treatment week 1	Treatment week 2
40 to <50	40 mg (4 tablets)	40 mg (4 tablets)
50 to <60	50 mg (5 tablets)	50 mg (5 tablets)
60 to <70	60 mg (6 tablets)	60 mg (6 tablets)
70 to <80	70 mg (7 tablets)	70 mg (7 tablets)
80 to <90	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 cladribine 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



12.14 Appendix 14: Signature Pages and Responsible Persons for the Trial

Signature Page – Protocol Lead

Trial Title:	A 2-year prospective study to evaluate the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis
EudraCT Number:	2017-002631-42
Clinical Trial Protocol Date / Version:	12 February 2019 / Version 2.0

Protocol Lead:

I approve the design of the clinical trial:

PPD

Signature

PPD

Date of Signature

Name, academic degree:	PPD
Function / Title:	PPD
Institution:	PPD
Address:	PPD
Telephone number:	PPD
E-mail address:	PPD

Signature Page –Coordinating Investigator

Trial Title	A 2-year prospective study to evaluate the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis
EudraCT Number	2017-002631-42
Clinical Trial Protocol Date / Version	12 February 2019 / 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 Council for Harmonisation Good Clinical Practice (Topic E6) and all applicable Health Authority requirements and national laws.

PPD

Signature

PPD

Date of Signature

Name, academic degree: PPD

Function / Title: PPD

Institution: PPD

Address: PPD

Telephone number: PPD

Fax number: PPD

Signature Page – Principal Investigator

Trial Title	A 2-year prospective study to evaluate the onset of action of Mavenclad® in subjects with highly active relapsing multiple sclerosis
EudraCT Number	2017-002631-42
Clinical Trial Protocol Date / Version	12 February 2019 / Version 2.0
Center 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 Council for 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 IMP 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

E-mail address: PPD

Name: PPD

Function / Title: PPD

Institution: Merck KGaA

Address: Alsfelder Str. 17, 64289 Darmstadt, Germany

Telephone number: PPD

E-mail address: PPD

12.15 Appendix 15: 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. Major 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 the trial country list: Denmark, Norway, Switzerland, and The Netherlands were removed; Belgium, Czech Republic, Hungary, Ireland, and Poland were added.	To reflect the current list of participating countries.
1 Synopsis 2 Sponsor, Investigators and trial Administrative Structure	The anticipated number of trial sites participating in this trial was changed from 100 to 80.	To reflect the current planned number of trial sites.
1 Synopsis	Planned trial period: The First Patient First Visit date was changed from Q1/2018 to Q2/2018 and the Last Patient Last Visit date was changed from Q3/2021 to Q1/2022.	Based on the progress of the trial, these milestones were updated.
1 Synopsis CCI [redacted]	CCI [redacted]	CCI [redacted]

1 Synopsis 8.1 Sample Size 12.9 Appendix 9: Blood Volumes	The planned number of subjects was changed from 300 to 265.	To reflect the current planned number of trial subjects.
1 Synopsis 4.1.1 Primary Endpoint(s) 8.1 Sample Size 8.3.1 Primary Endpoint(s) 8.5.2 Analysis of Primary Endpoint(s)	Primary endpoint: added clarification on sequential order of testing procedures; revised the primary endpoint analyses and revised the primary population for analyses from the ITT Set to the FAS.	To describe the statistical model to be used for primary analysis in more detail.
1 Synopsis 5.8 Planned Extension Studies 6.13 Medical Care of Subjects After End of Trial 12.4.6.1 Determination of sample size 12.5.6.1 Determination of sample size	The statement that all subjects would be offered the chance to participate in optional sub-studies was slightly reworded to be more vague.	Due to budgetary constraints and logistics reasons, the number of participants is restricted to 50 per sub-study. This is explicitly stated in the respective appendices that provide detailed information on these sub-studies.

1 Synopsis 4.3.1 Tertiary Endpoints 8.3.3 Tertiary Endpoints 8.5.3 Tertiary Endpoints	Added clarification that changes in CUA lesions compared to the Baseline period will be analyzed for the periods of Month 6 to Month 12, Month 1 to Month 12, Month 18 to Month 24, and Month 1 to Month 24. Also, it was clarified that further periods and comparisons may be defined in the SAP. Addition of further tertiary endpoints: • Number of CUA lesions during the Baseline and post-Baseline periods • Changes in active T1 Gd+ lesion count at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to Baseline • Volume changes of T1 gadolinium (Gd)+ lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline • Number of T1 hypointense lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline • Change in volume of T1 hypointense lesions at the end of 1, 2, 3, 6, 12, 15, 18 and 24 months compared to baseline • Changes in new T2 lesion count during the post-Baseline periods compared to the Baseline period Responder rate during the different periods with responder being defined as subjects with a CUA lesion count reduction of at least 1 Clarification for the analysis or tertiary endpoints	Revised to provide more detailed information on the time periods to be analyzed. Amended to include more tertiary endpoints.
1 Synopsis 5.3.2 Exclusion Criteria	Certain key exclusion criteria included in the synopsis were updated to reflect changes to exclusion criteria below.	

	Number 4: Revised to clarify that the presence of signs of PML detected by MRI, clinical and/or biomarker evaluations would lead to exclusion of the subject. Other major Central Nervous System disease clinically diagnosed or evidenced in screening MRI is also included.	To clarify that suspect of PML alone does not constitute a reason for excluding a subject. To clarify that signs of PML can be either be detected by MRI, by clinical, and/or by biomarker analysis.
	Number 5 and 6: HIV and hepatitis criterion split out. Revised Criterion Number 6 to add further tests to confirm hepatitis B infection (positive anti-hepatitis B surface antibody [anti-HBs Ab] and/or hepatitis B core antibody [total anti-HBcAb]) confirmed by a positive viral PCR). Positive core antibody test for IgG and or IgM was removed from Exclusion Criterion number 5. Number 7: Clarification was added to confirm that only subjects with active tuberculosis (TB) or who were undergoing current treatment for latent TB infection were to be excluded. Number 9: Updated to include a risk-benefit evaluation for subjects with prior malignancy. Number 13: Revised to exclude subjects with moderate or severe renal impairment (defined as having a creatinine clearance of <60 mL/min). Addition of new criterion Number 14: Moderate or severe hepatic impairment confirmed as per the standards of local clinical practice (for example, Child-Pugh score >6).	To further specify methods for confirmation of hepatitis B infection. To meet SmPC specifications. To comply with contraindications for Mavenclad® as described in the current SmPC (current in Feb 2018): The revision was made to meet the SmPC specifications regarding renally impaired subjects receiving Mavenclad® and with regard to safety prerequisites for the use of gadolinium. Added to exclude subjects with moderate or severe hepatic impairment based on the safety profile of Mavenclad®.
5.3.1 Inclusion Criteria	Number 5: Revised to introduce Appendix 12, which provides a list of highly effective birth control methods. In addition, definitions of WOCBP, postmenopausal women, and surgically sterile women were added.	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 6.5.4 Special Precautions 7.4.3 Clinical Laboratory Assessments, Table 1 Local Laboratory Assessments 12.1 Appendix 1 Schedule of Assessments	Addition of new criterion Number 8: Serology assessment for varicella was added. Furthermore, it was clarified (in Inclusion Criterion #8 as well as in the Special Precautions section), that subjects who are antibody-negative shall receive vaccination 4 to 6 weeks prior to initiation of cladribine therapy. Varicella virus testing was added to the list of Local Laboratory Assessments and to the appropriate footnote below the Schedule of Assessment.	Inclusion criterion was added to include subjects with previous exposure and immunity to varicella virus. Respective revisions were made throughout the protocol where appropriate.
5.5.1 Withdrawal from Trial Therapy	In the list of cases that lead to mandatory withdrawal, the terminology was changed from "evidence or suspect of PML" to "presence of signs of PML detected by MRI, clinical and/or biomarker evaluations".	To clarify that suspect of PML alone does not constitute a reason for excluding a subject (as also reflected in the revision of Exclusion Criterion number 4).
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.
6.12 Treatment of Overdose	SAE report form was replaced with the eCRF report page wherever applicable.	In order to ensure proper documentation of the events, the eCRF page will be used in the study.
7 Trial Procedures and Assessments	Added information that subjects will be assigned a 10-digit identification number via IRT.	To clarify the process of subject number allocation.
7.1.1 Pre-baseline Screening (-3 months)	Revised to add registration with IRT for shipment of medication to the site. Added varicella to serology. Deletion of the instruction to repeat lymphocyte count within 4 weeks of Baseline in cases where lymphocyte count at Screening was done before 4 weeks from Baseline.	In order to clarify processes for trial supply and serology analyses, and to remove redundant instructions.
7.4.3 Clinical Laboratory Assessments Table 3 Local Laboratory Assessments	Pregnancy test was added to the list of local laboratory assessments at baseline.	To clarify that both urine and serum pregnancy test are acceptable.

7.1.3 Baseline Visit (Study Day 1)	Added a time window of +7 days for performing this visit. Specified that the number of relapses experienced by the subjects should be recorded for the last 12 months. Added the instruction to repeat lymphocyte count within 4 weeks of Baseline in cases where lymphocyte count at Screening was done before 4 weeks from Baseline.	To define a time window for conducting the Baseline Visit after Pre-Baseline Screening. To provide clarification on data collection. To provide further clarification on trial conduct/processes to be followed for laboratory analyses.
7.1.3 Baseline Visit (Study Day 1) (+7 days) 7.1.4 Month 1 Visit (± 7 days) 7.1.8 Month 12 Visit (± 7 days) 12.1 Appendix 1 Schedule of Assessments	IWRS was replaced by IRT. In addition, IRT contact has been added to Pre-baseline Screening.	IWRS will no longer be used in this trial. reference to the now to be used IRT were made throughout the protocol where appropriate.
7.3.1.1 Schedule	Text regarding restrictions for MRI schedule was updated.	The restrictions for the MRI schedule have been clarified to allow for the collection of data under real life conditions and to avoid missing data. This will allow to evaluate the potential impact of steroid or ACTH administration or a relapse on MRI outcome variables.
7.3.1.2 Scanning: MRI Scanning Procedures	Revised the definition of "active lesions".	To provide more clarity on key aspects of MRI scanning procedures relevant for this trial.
7.3.2 Clinical Assessments	The definition of EDSS progression was clarified.	Change made for clarification.
CCI [redacted]	CCI [redacted]	CCI [redacted]
8 Statistics	Section 8 (including several sub-sections) was amended to provide more detail on the planned analyses.	Major updates were made to the statistics sections in order to: • further define the analyses of all endpoints and to add robustness analyses for the primary endpoint(s) • further define the analyses of the tertiary endpoints and to add further tertiary endpoints • further define the analysis sets

11 References Cited in the Text	The list of references was corrected to list all references cited in the text.	Amended for completeness and correctness.
12.1 Appendix 1 Schedule of Assessments	Added visit window of +7 days for Baseline. Re-labelled End of treatment to Early termination. Replaced IWRS with IRT. Added IRT contact to Pre-Baseline Screening. Updated the list of abbreviations. Revised the footnote referring to local laboratory test to add test for varicella. Revised the footnote referring to neurofilament to clarify timing of the analysis.	Revised/amended to reflect revisions made to the description of the trial visits and to provide further clarification on the trial conduct and the timing of assessments for the Investigator.
CCI [redacted]		

CCI [redacted]

12.8 Appendix 8 Expanded Disability Status Score (EDSS)	Corrected in-text table displaying EDSS scoring.	To provide correct information.

CCI [redacted]

Section 12.12 Appendix 12 Birth control methods which may be considered as highly effective	The appendix was added to provide a list of birth control methods which may be considered as highly effective	To provide clarification to the Investigator regarding the meaning of "effective contraceptive measures", to educate subjects participating in the trial, and, ultimately, to avoid possible human teratogenicity due to the use of Mavenclad®.
Section 12.13 Appendix 13 Mavenclad Posology	The appendix was added to provide detailed information on how Mavenclad® dosing (number of 10 mg tablets) is to be performed based on the subject's body weight, per treatment week and per week day.	To provide clarification to the Investigator regarding exact, weight-based dosing of Mavenclad® to ensure that the recommended cumulative dose of 3.5 mg/kg bodyweight over 2 years will not be exceeded.
12.14 Appendix 14 Signature Pages and responsible Persons for the Trial	Information on Sponsor responsible persons not named on the cover page was revised.	To provide correct and current information.
	Some minor typos and inconsistencies were corrected in the protocol.	

CCI ; CUA=combined unique active; DMD=disease modifying drug; eCRF=electronic case report form; EDSS=Expanded Disability Status Score; EMA=European Medicines Agency; GD=gadolinium; FAS=Full Analysis Set; CCI M; IMP=investigational medicinal product; IRT=interactive response technology; ITT=Intention-to-treat; IWRS=Interactive Web Response System; MRI=magnetic resonance imaging; CCI ; CCI ; PML=progressive multifocal leukoencephalopathy; SAE=serious adverse event; SAP=Statistical Analysis Plan; SmPC=summary of product characteristics; WOCBP=women of childbearing potential.

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	12 February 2019