Effect of MD1003 in progressive multiple sclerosis:
a randomized double-blind placebo-controlled study

CLINICAL TRIAL PROTOCOL

Version No: 4 **Dated 12-Nov-2018**

Short title:	**SPI2**
Product:	**MD1003**
Protocol No:	**MD1003CT2016-01MS-SPI2**
EudraCT No:	**2016-000700-29**
IND Number:	**118798**
SPONSOR:	**MEDDAY PHARMACEUTICALS SA**

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SPONSOR SIGNATURE

The study protocol of the clinical trial "Effect of MD1003 in progressive multiple sclerosis: a randomized double-blind placebo-controlled study" version 4 dated 12 Nov 2018 was subjected to critical review and the information it contains is consistent with current knowledge of the risks and benefits of the investigational product. My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

Name	Title	Date	Signature
Frederic Sedel, MD, PhD	Chief Scientific Officer	12-Nov-2018	
Frederick Munschauer, MD	Global Head of Medical	12-Nov-2018	
Prof. Bruce Cree, MD, PhD, MAS	Coordinating Investigator	12-Nov-2018	

CRO and designees

Monitoring, data management, statistical analysis: **Parexel International (Dublin, Ireland)**

Cardiac Safety Central Laboratory: **Banook (Nancy, France)**

Core Imaging Laboratory: **NeuroRx (Montreal, Canada)**

Clinical Central Laboratory: **Eurofins (Lancaster, USA/Breda, The Netherlands/Singapore, Asia)**

Independent Biotin Assay Laboratory: **Atlanbio (Saint Nazaire, France)**

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INVESTIGATOR SIGNATURE

My signature, in conjunction with the signature of the sponsor, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, the International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the Code of Federal Regulations (CFR), the ethical principles that have their origins in the Declaration of Helsinki, and applicable privacy laws.

I have fully discussed the objectives of this study and its contents with the sponsor's representatives. I agree to conduct this study according to the protocol and its amendments and to comply with the requirements of the patient ethical, legal and safety considerations.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care under applicable regulations.

Name	**Title**	**Date**	**Signature**
	Principal Investigator		

STUDY SUMMARY

Study Protocol Title	Effect of MD1003 in progressive multiple sclerosis: a randomized double-blind placebo-controlled study
Short title	SPI2
Clinical Phase	Phase III
Study Protocol Number	**MD1003CT2016-01MS-SPI2**
EudraCT Number	**2016-000700-29**
Methodology and study design	**PART 1**: Total duration of Part 1 is 27 months. The randomized double-blind placebo-controlled period ranges from 15 to 27 months depending upon the randomization date of an individual patient. Once the last month 15 evaluation of the study has been completed, patients will switch to the active drug at the next planned visit. Participants and study personnel will remain blinded as to the original treatment assignment. Maximum duration of double-blind period per patient will be no longer than 27 months. **PART 2**: At the last evaluation of Part 1 (Visit 11/Month 27) all participants will be offered active treatment in an open label extension for 39 additional months (From V11/M27 to V18/M66). The purpose of the active drug extension is to further define the safety of MD1003.
Study Centers	**Coordinating investigator**: **Prof. Bruce CREE, UCSF, USA** **Investigational centers**: 90 centers located in North America (USA/Canada), Europe and Australia**.** **Steering committee**: Prof. Fred LUBLIN, New York, USA; Prof. Bruce CREE, San Francisco, USA; Prof. Gary CUTTER, Birmingham, USA; Prof. Jerry WOLINSKY, Houston, USA; Prof. Mark FREEDMAN, Ottawa, Canada; Prof. Giancarlo COMI, Milan, Italy; Prof. Gavin GIOVANNONI, London, UK**;** Prof. Hans-Peter HARTUNG, Düsseldorf, Germany. **Data Safety Monitoring Board:** Prof. Stephen REINGOLD, Salisbury, USA; Prof. Pierre DUQUETTE, Montreal, Canada; Prof. Tobias DERFUSS, Basel, Switzerland; Prof. Franz FAZEKAS, Graz, Austria; Prof. Maria Pia SORMANI, Genoa, Italy.

Objectives	**Primary objective** To demonstrate the superiority of MD1003, 300 mg/day, over placebo to clinically improve patients with progressive multiple sclerosis (MS). **Secondary objectives** To evaluate the safety of MD1003
Number of patients	Approximately 600 patients divided into 2 groups: - Group 1 (300 patients): Placebo - Group 2 (300 patients): MD1003, 300 mg/day
Diagnosis and inclusion criteria	1. Patient aged 18-65 years old 2. Signed and dated written informed consent form in accordance with local regulations: having freely given their written informed consent to participate in the study 3. Diagnosis of primary or secondary progressive MS fulfilling revised McDonald criteria (2010) and Lublin criteria (2014) 4. Documented evidence of clinical disability progression within the 2 years prior to inclusion, i.e. a) progression of EDSS during the past two years of at least 1 point sustained for at least 6 months if inclusion EDSS is from 3.5 to 5.5 or at least 0.5 point increase sustained for at least 6 months if inclusion EDSS is from 6 to 6.5 or b) increase of TW25 by at least 20% in the last two years sustained for at least 6 months or c) other well-documented objective worsening validated by the Adjudication Committee 5. EDSS at inclusion from 3.5 to 6.5 6. TW25 < 40 seconds at inclusion visit 7. Kurtzke pyramidal functional subscore ≥2 defined as "minimal disability: patient complains of motor-fatigability or reduced performance in strenuous motor tasks (motor performance grade 1) and/or BMRC grade 4 in one or two muscle groups"
Exclusion criteria	1. Clinical evidence of a relapse in 24 months prior to inclusion 2. Treatment with any product containing biotin as single ingredient within six months prior to inclusion (multivitamin supplementation authorized if biotin < 1mg per day) 3. Concomitant treatment with fampridine at inclusion or in the 30 days prior to inclusion 4. New immunosuppressive/immunomodulatory drug initiated less than 90 days prior to inclusion 5. Treatment with botulinum toxin (except for cosmetic purposes) initiated within 6 months prior to inclusion 6. In-patient rehabilitation program within the 3 months prior to inclusion 7. Pregnancy, breastfeeding or women with childbearing potential without acceptable form of contraception

	8. Men unwilling to use an acceptable form of contraception 9. Any general chronic handicapping/incapacitating disease other than MS 10. Any serious disease necessitating biological follow-up with biological tests using biotinylated antibodies or substrates 11. Past history of rhabdomyolysis or metabolic myopathy 12. Known fatty acids beta oxidation defect 13. Known hypersensitivity or intolerance to biotin, analogues or excipients, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption 14. Patients with hypersensitivity or any contra-indication to gadolinium 15. Patients with uncontrolled hepatic disorder, renal or cardiovascular disease, or cancer 16. Laboratory tests out of normal ranges considered by the investigator as clinically significant with regards to the study continuation 17. Patients with history or presence of alcohol abuse or drug addiction 18. Untreated or uncontrolled psychiatric disorders, especially suicidal risk assessed by Columbia-Suicide Severity Rating Scale (C-SSRS) 19. Participation in another research study involving an investigational product (IP) in the 90 days prior to inclusion, or planned use during the study duration 20. Patients likely to be non-compliant to the study procedures or for whom a long-term follow-up seems to be difficult to achieve 21. Relapse that occurs between inclusion and randomization visit
Investigational Product	MD1003 300 mg/day (100 mg tid).
Control therapy	Placebo capsules in placebo arm for at least 15 months and up to 27 months depending on the patient randomization date
Concomitant & intercurrent therapies	• Usual care including immuno-modulators, and immunosuppressive drugs including monthly pulses of IV methylprednisolone allowed in placebo and treated groups if already treated by these drugs • IV methylprednisolone allowed during the trial if relapse without oral taper • Fampridine not allowed during the study • Initiation of botulinum toxin not allowed during the study (except for cosmetic purpose) • In-patient rehabilitation therapy program not allowed during the study

Duration of administration	**PART 1**: Total duration of Part 1 is 27 months. The randomized double-blind placebo-controlled period ranges from 15 to 27 months depending upon the randomization date of an individual patient. Once the last month 15 evaluation of the study has been completed for all subjects, participants will switch to the active drug at the next planned visit (V8/M18 or V9/M21 or V10/M24). After switching to active drug, participants and study personnel will remain blinded as to the original treatment assignment. The maximum duration of double-blind period per patient will be no longer than 27 months. **PART 2**: At the last evaluation of Part 1 (Visit 11/Month 27) all participants will be offered active treatment in an open label extension for 39 additional months (From V11/M27 to V18/M66). The purpose of the active drug extension is to further define the safety of MD1003.
Evaluation criteria	• **Primary efficacy endpoint** Proportions of patients: • with decreased EDSS at M12 confirmed at M15 (where decreased EDSS is defined as a decrease of at least 1 point if initial EDSS from 3.5 to 5.5 and of at least 0.5 point if initial EDSS from 6 to 6.5) or • with improved TW25 of at least 20% at M12 confirmed at M15 The baseline score for EDSS will be the lowest (best) value obtained during either the inclusion or randomization visit. The baseline value for TW25 will be the best mean of the 2 scores obtained at either the inclusion or randomization visit (the lowest mean value between the 2 visits). The TW25 value at visit M12 and M15 is defined as the mean of the two TW25 attempts at each visit. • **Secondary efficacy endpoints** 1. Time to EDSS progression confirmed at 12 weeks 2. Mean difference between treatment arms in CGI at M15 3. Mean difference between treatment arms in SGI at M15 4. Mean change in TW25 score between M0 and M15 • **Exploratory endpoints** 1. Mean change in Brain MRI measures between M0 and M15: a. Percent whole brain volume b. Percent thalamic volume

	c. Percent cortical grey matter volume d. Brain water content evaluated by Pseudo T2 relaxation time e. NAA/Cr in a subset of sites acquiring MRS 2. Remote monitoring of ambulation 3. Multiple Sclerosis Quality of Life-54 (MSQOL54) and Caregiver health-related quality of life in Multiple Sclerosis (CAREQOL-MS) subscores and composite scores 4. Subscores of the Kurtzke functional score 5. Symbol Digit Modalities Test (SDMT) • **Safety evaluation** 1. Recording of AEs 2. Laboratory testing (standard haematology and biochemistry panel) 3. ECG: PR, QRS, QT and RR interval, HR and QTcF, wave morphology, rhythm and conduction 4. Brain MRI: new or enlarging T2 lesions and Gd+ lesions 5. Columbia-Suicide Severity Rating Scale
Statistical methodology	For the sample size estimation of SPI2, hypotheses were set at 2% for the proportion of clinically improved patients in the placebo group and at 12% in the MD1003 group. A sample-size of 600 patients will provide a power >90% in the global population. A logistic regression will be fitted to estimate the treatment effect (odd-ratio of improved patients) using treatment, disease history (SPMS/PPMS) and geographical region as fixed factors (referred as the main logistic model in the following parts). The main logistic model will then be used for each component of the composite outcome (EDSS and TW25 responses), to complement the analysis of the main endpoint. For the primary endpoint analysis, patients without confirmation of clinical response at M12 and M15 will be considered as non-responders (missing data will be handled in accordance with the rules specified in the statistical analysis plan). No multiplicity adjustment is considered for the primary endpoint as there is a unique main criterion. Secondary endpoints are hierarchically scaled by order of clinical importance.
Duration of patient participation	**PART 1**: 28 months (1-month screening plus at least 15-months, but not to exceed 27 months of blinded study drug administration) **PART 2**: Open label extension for 39 months (V11/M27 to V18/M66)
Study duration	Total study duration: 84 months Recruitment period: 17 months recruitment **PART 1**: 28 months (1-month screening period + 27-month patient participation) **PART 2**: 39 months from V11/M27 until V18/M66

LIST OF ABBREVIATIONS

9-HPT	Nine Hole Peg Test
ACC	Acetyl-CoA Carboxylase
AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
APPT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
ATP	Adenosine Triphosphate
BBGD	Biotin Basal Ganglia Disease
BNB	Bisnorbiotin
BSO	Biotin Sulfoxide
CAC	Clinical Adjudication Committee
CSCL	Core Cardiac Safety Laboratory
CAREQOL-MS	Caregiver health-related quality of life in Multiple Sclerosis
eCRF	electronic Case Report Form
CIS	Clinically Isolated Syndromes
C-SSRS	Columbia-Suicide Severity Rating Scale
CGI	Clinical Global Impression assessed by Investigator
CNS	Central Nervous System
CPT1	Carnitine Palmitoyltransferase 1
DSMB	Data Safety Monitoring Board
EC	Ethics Committee
ECG	Electrocardiography
EDSS	Expanded Disability Status Scale
ETDRS	Early Treatment Diabetic Retinopathy Study
FAS	Full Analyzable Set
FDA	Food and Drug Administration
FIS	Fatigue Impact Scale
FS	Functional System
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transpeptidase
GP	General Practitioner
HEENT	Head, Eyes, Ears, Nose, Throat
H-MRS	Proton Magnetic Resonance Spectroscopy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee

IP	Investigational Product
IRB	Institutional Review Board
ITT	Intent-To-Treat
IVMP	Intravenous Methylprednisolone
IWRS	Interactive Web Response System
LOCF	Last Observation Carried Forward
MCC	3-Methylcrotonyl-CoA Carboxylase
MRI	Magnetic Resonance Imaging
MRS	Magnetic Resonance Spectroscopy
MS	Multiple Sclerosis
MSQOL 54	Multiple Sclerosis Quality of Life-54
MSWS	Multiple Sclerosis Walking Scale
NAA/Cr	N-acetylaspartate / creatine ratio
NIP	Non-Investigational Product
OLE	Open Label Extension
ON	Optic Neuritis
PP	Per-Protocol
PC	Pyruvate Carboxylase
PCC	Propionyl-CoA Carboxylase
PPMS	Primary Progressive Multiple Sclerosis
PT	Prothrombin Time
RBC	Red Blood Cell
RRMS	Relapsing-Remitting Multiple Sclerosis
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis plan
SDMT	Symbol Digit Modalities Test
SGI	Clinical Global Impression assessed by Subject
SPMS	Secondary Progressive Multiple Sclerosis
T3	Triiodothyronine
TCA	Tricarboxylic Acid
TSH	Thyroid-stimulating Hormone
TW25	Timed 25-Foot Walk
USA	United States of America
VA	Visual Acuity
WBC	White Blood Cell

TABLE OF CONTENTS

INTRODUCTION / RATIONALE

Multiple Sclerosis (MS) is a common neurological disease affecting more than 2 million people worldwide. Its prevalence rate varies between races and regions, with an estimated mean of around 1/1,000 in Europe and United States of America.

MS is an inflammatory autoimmune disease that damages the myelin of the central nervous system (CNS) causing neurological impairment and, in many cases, severe disability (Noseworthy *et al.*, 2000).

The aetiology of MS remains unknown. It is generally believed that MS is mediated by a complex interplay between host genetic factors and environmental exposures, such as viral infection and hypovitaminosis D (Sotgiu *et al.*, 2004).

Approximately 85% of all patients present with relapsing-remitting (RRMS), which is characterized by unpredictable acute episodes of neurological dysfunction named relapses, followed by variable recovery and periods of clinical stability.

Around 15% of all patients develop a sustained deterioration of their neurological function from the beginning; i.e. primary progressive multiple sclerosis (PPMS) (Bradl & Lassmann, 2009).

Within 15 years more than 50% of patients who presented with a RR form develop sustained deterioration with or without superimposed relapses; this form is called secondary progressive (SPMS). Conversion of RRMS to secondary progressive presentations of MS is an age-dependent process with a rate estimated at 2-3% per year (Confavreux & Vukusic, 2006).

The term “relapsing MS” includes 1) RRMS, and 3) clinically isolated syndromes (CIS) who show dissemination of lesions in time and space on magnetic resonance imaging (MRI) scans according to the 2010 revised McDonald’s criteria (Lublin *et al.*, 2014, Polman *et al.*, 2011). All the disease modifying therapies approved so far in MS are intended to treat relapsing forms of MS. Prevention and/or modification of relapses as well as prevention or delay of the accumulation of lesions and disability due to relapses have constituted the main goals in the treatment of relapsing multiple sclerosis.

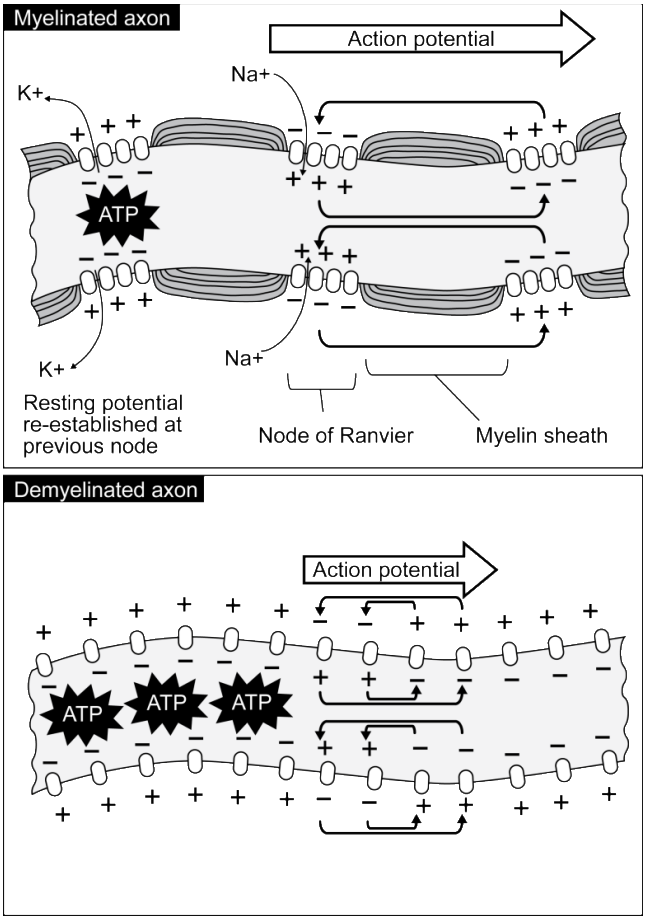
In relapsing MS, lymphocytes and monocytes of the peripheral adaptive immune system infiltrate perivascular brain and spinal cord tissue causing focal inflammation that can be identified on imaging as acute contrast enhancing lesions. The histopathological hallmark of these lesions is injury to oligodendroglia cells that wrap axons in myelin, the cell membrane that enhances electrical resistance and allows salutatory conduction through the central nervous system. Axons themselves are typically relatively spared and this feature helps distinguish multiple sclerosis from tissue destructive processes. Thus in this relapsing, inflammatory phase, MS is considered to be an inflammatory demyelinating disease. The focal inflammation resolves over weeks and gliosis follows resulting in the hardened plaques described at autopsy.

The term “progressive MS” includes both PPMS and SPMS (Lublin *et al.*, 2014). Progressive MS can be “active” when clinical relapses and/or MRI activity (contrast-enhancing lesions; new and unequivocally enlarging T2 lesions) occur. Progressive MS is said to be “not-active” in the absence of clinical relapses or MRI inflammatory activity.

Both inflammatory and neurodegenerative processes contribute to progressive MS with a continuum between progressive active forms where inflammation still exist and not-active forms where the axonal degenerative process predominates without overt signs of focal inflammation. To date most therapeutic approaches of progressive MS focused on the inflammatory component with little success (Ontaneda *et al.*, 2015). In contrast the axonal degenerative process, which is far less well understood, has been the focus of only a few trials (Chataway *et al.*, 2014, Kapoor *et al.*, 2010).

At the cellular level, it has been hypothesized that progressive axonal degeneration might be linked to/driven by secondary energy failure. Indeed, it is believed that, in the normal condition, myelin insulation reduces the energy demand during impulse propagation because adenosine triphosphate (ATP) is needed to reform the resting membrane potential only at the Ranvier nodes. Demyelinated

Figure 2. Increased axonal energy demand as a result from axon demyelination. Nerve impulses in myelinated axons propagate between the nodes of Ranvier. Depolarization of the membrane is triggered by the transient opening of voltage-gated Na^+ ion channels. Repolarization is achieved through voltage-gated K^+ ion channels, which restore electrical conditions, followed by restoration of the ionic distribution by the ATP-dependent Na^+/K^+ ATPase pump. ATP consumption is greatly increased in demyelinated axons due to redistribution of ion channels along the length of the denuded axon.



The figure above illustrates the increased axonal demand as a result from axonal demyelination. Nerve impulses in myelinated axons propagate between the nodes of Ranvier. The transient opening of voltage-gated Na^+ ion channels triggers depolarization. Repolarization is achieved through voltage-gated K^+ ion channels, which restore electrical conditions, followed by restoration of the ionic distribution by the ATP-dependent Na^+/K^+ ATPase pump. ATP consumption is greatly increased in demyelinated axons due to redistribution of ion channels along the length of the denuded axon.

fibers are placed at an energetic disadvantage because of increased ionic leaks across the denuded axon membrane, resulting in an increased energy demand for ion pumping. In addition, energy production may be compromised owing to mitochondrial disruption and Na+–K+–ATPase–mediated ion transport may be reduced in many demyelinated axons in the MS brain that could bias these axons towards a state of 'virtual hypoxia'. The resulting mismatch between energy supply and demand could result in degeneration (Luessi *et al.*, 2012, Stys *et al.*, 2012).

1. *Vitamin H/Biotin: mechanism of action*

Vitamin H, more commonly known as biotin, is part of the water-soluble B complex vitamin group. Biotin is an essential nutrient that acts as a carboxyl (CO_2) transporter in carboxylation reactions. In mammals, biotin serves as a cofactor for four carboxylases involved in the metabolism of carbohydrates, amino acids and fatty acids: (1) pyruvate carboxylase (PC), (2) 3-methylcrotonyl-CoA carboxylase (MCC), (3) propionyl-CoA carboxylase (PCC) and (4) acetyl-CoA carboxylase (ACC) (Tong, 2013). Three out of these four reactions lead to production of Krebs cycle intermediates that are central in

aerobic energy production. In addition, ACC is the rate-limiting enzyme for fatty acids synthesis and is expressed at high level in oligodendrocytes. It is hypothesized that activation of ACC by high doses of biotin could stimulate remyelination.

Besides its role as a co-factor, biotin may regulate genes encoding enzymes or transporters involved in its own metabolism or other cell functions (Zempleni *et al.*, 2009). However, this physiological role of biotin remains unclear.

High doses of biotin are expected to be the first therapeutic approach having an impact on progressive MS by reversing the "virtual hypoxia" phenomenon and triggering remyelination (Sedel *et al.*, 2015a, Sedel *et al.*, 2015b).

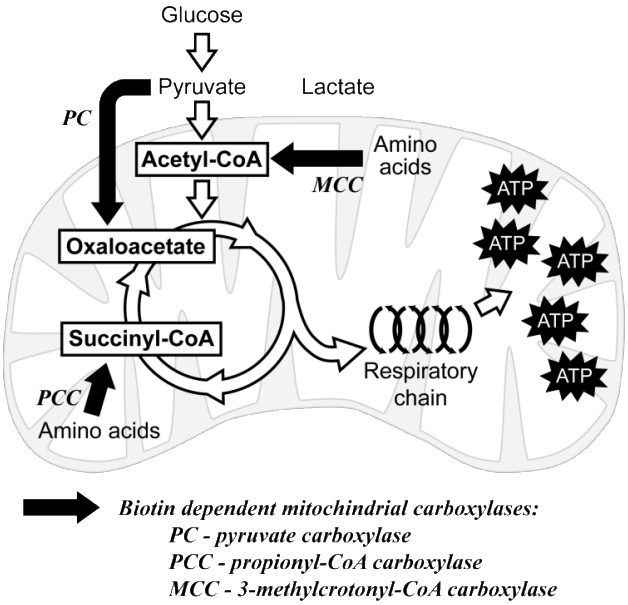
Target 1, increasing the amount of ATP in the diseased neurons: Reversing the virtual hypoxia phenomenon.

- It is hypothesized that the treatment with high-dose biotin reverses the state of virtual hypoxia through its role as a cofactor for PC, MCC, and PCC. These three enzymes are central to aerobic energy production and generate intermediates for the tricarboxylic acid (TCA) cycle. All three of these enzymes are expressed in astrocytes and neurons. PC catalyzes the conversion of pyruvate to oxaloacetate, thus serving an essential anaplerotic role by replenishing the 4-carbon "backbone" of the TCA cycle. PCC generates methylmalonyl-CoA from propionyl-CoA, which is then converted to succinyl-CoA by methylmalonyl-CoA mutase. MCC plays a role in the metabolism of leucine and ultimately leads to production of acetyl- CoA. Thus, these three biotin-dependent carboxylases feed the TCA cycle at three different entry points: oxaloacetate, succinate and acetyl-CoA, and could be expected to increase the levels of cellular ATP. By increasing the available intraneuronal pool of ATP, high-dose biotin may reduce demyelinated neural dysfunction and the adverse effects of hypoxia.

Sedel et al, Neuropharmacology submission 2015

- The first evidence that high doses of biotin (5 to 10 mg/Kg/day) could have an advantage to low doses (0.014 mg mg/Kg/day) was supported by previous experience in "Biotin basal ganglia disease" (BBGD), a disorder of energy metabolism. BBGD is caused by mutations in the thiamine transporter THTR2 (Debs *et al.*, 2010, Ozand *et al.*, 1998, Zeng *et al.*, 2005). A thiamine defect is expected to block the Krebs cycle (Subramanian *et al.*, 2006). High doses of Biotin (about 5-10 mg/kg/day) showed potential efficacy in this orphan neurological disease.

Figure 3. Biotin increases ATP production in axonal mitochondria (Fernandez-Mejia, 2005)



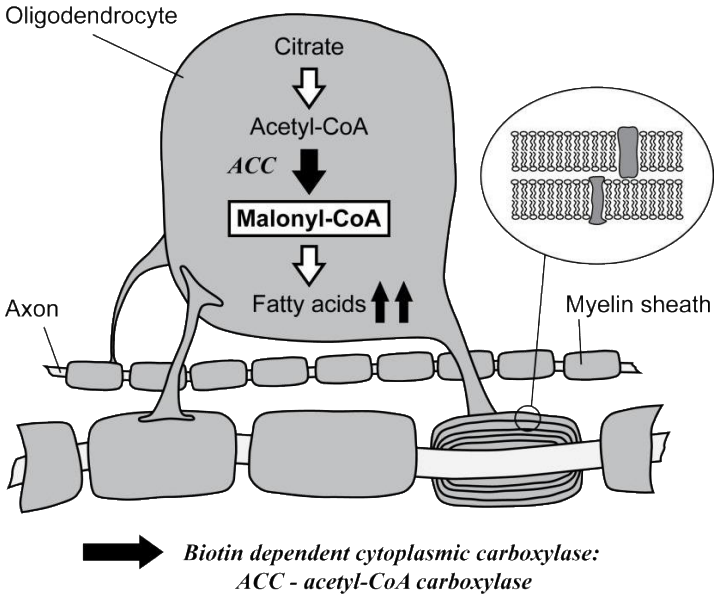
The figure describes how biotin increases ATP production in axonal mitochondria (Sedel et al., 2015b).

Target 2: Triggering remyelination

A second biotin-dependent pathway that occurs in the cytoplasm through the biotin-dependent ACC1 and ACC2 may play a role in myelin repair. This pathway is key in the regulation of fatty acid synthesis (Tong, 2013). ACC1 and ACC2 are key regulators of membrane lipid synthesis including myelin synthesis (Chakraborty & Ledeen, 2003). In the CNS, ACC1 and 2 are mostly expressed in oligodendrocytes (Chakraborty & Ledeen, 2003). Furthermore, ACC can be detected in purified myelin (Chakraborty & Ledeen, 2003).

Figures and Tables

Figure 1: Biotin activates myelin formation in oligodendrocytes through its role as a cofactor for ACC (Chakraborty et al., 2003)



The figure summarizes how biotin activates myelin formation in oligodendrocytes through its role as a cofactor for ACC (Sedel *et al.*, 2015a).

2. Clinical evidence for biotin as a potential treatment for progressive MS

1) Pilot, open-label study in patients with progressive MS

Twenty-three consecutive patients with progressive MS were treated with high doses of biotin ranging from 100 mg to 600 mg/day (median= 300 mg/day divided in three doses) in a compassionate use protocol (Sedel *et al.*, 2015b). Treatment duration was 2 to 36 months (mean treatment duration = 9.2 months). Patients were followed in three different MS-reference centers in France. Most of the patients had been treated with medications that failed to improve their neurological condition including monthly pulses of intravenous methylprednisolone (IVMP), cyclophosphamide, azathioprine or fampridine that are sometimes used in empiric treatment of progressive MS. None of these drugs were initiated during the period of treatment with biotin, except consecutive pulses of IVMP in case of superimposed MS relapses.

Fourteen patients were classified as PPMS and 9 as SPMS. Four patients had permanent visual loss following optic neuropathies; one patient had progressive lateral hemianopia caused by involvement of the optic radiations and 18 patients had progressive paraparesis or tetraparesis related to spinal cord involvement.

Overall, 21/23 patients with progressive MS (91.3%) exhibited clinical improvement with high doses of biotin evidenced with clinical, electrophysiological and proton magnetic resonance spectroscopy (H-MRS) data. In all cases, clinical improvement appeared 2 to 8 months (mean=3 months) following

treatment initiation. Only 2 patients with severe tetraparesis did not show positive response to treatment, possibly related to short duration of treatment exposure (8 and 7 months respectively). However, one patient with a severe tetraparesis appeared to benefit after only 8 months of treatment. The dose of 300 mg/day was associated with the best clinical efficacy. In addition, treatment appeared to be safe: transient diarrhoea, the only minor adverse effect, was noted in 2 patients. One patient died at 73 years old, from cardiac failure three years after treatment onset, but this was not attributed to treatment. No symptoms of cardiac dysfunction were observed in the 22 other patients. MS relapse frequency was similar to that observed before treatment in the four patients who experienced at least one relapse.

2) Randomized, double-blind, placebo-controlled trial in adult patients with progressive MS (MS-SPI)

MS-SPI the first randomized, double-blind study conducted by MedDay was intended to demonstrate the superiority of D-Biotin 300 mg/day over placebo in clinical confirmed improvement of patients with not active progressive multiple sclerosis (PPMS or SPMS) based on EDSS and timed 25-foot walk (TW25) measures. This was a 12-month double-blind randomized placebo-controlled Phase 2b/3 trial that compared MD1003 (D-Biotin 300 mg/day) with placebo followed by a 12 month-extension phase during which the placebo was switched to the active drug (during the extension phase patients and clinicians remained blinded to the treatment received during the double-blind phase). D-Biotin was administered orally at a dose of 100 mg thrice daily (morning, noon, evening). Eligible patients were 18 to 75 years of age with PPMS or SPMS that fulfilled revised McDonald (Polman *et al.*, 2011) and Lublin (Lublin & Reingold, 1996) criteria with clinical evidence of spastic paraparesis (walking disability due to cortico-spinal tracts involvement). Patients with clinical or radiological evidence of inflammatory disease activity within the previous year were excluded. All patients had a baseline EDSS of 4.5 to 7 with evidence of disease progression during the previous two years (an increase of EDSS of ≥1 point if EDSS was 4.5–5.5 and ≥0.5 point if EDSS was 6–7). The primary endpoint was the proportion of patients with a clinical improvement in either EDSS or timed 25-foot walk (TW25) scores at month 9 (and confirmed at month 12) compared with the best EDSS/TW25 values recorded between screening and randomization visits. Clinical improvement was defined as a decrease of ≥0.5 points or ≥ 1 point for EDSS (if baseline score was 6–7 or 4.5–5.5, respectively) or a decrease of ≥20% for TW25 score.

Secondary endpoints were the mean change in EDSS from randomization to month 12; the proportion of patients with EDSS progression from randomization to month 9 (confirmed at month 12); mean change in TW25 (randomization to month 12); the clinical global impression of change score evaluated by the investigator (CGI) and the subject (SGI) at month 12; and mean change in MS walking scale (MSWS), fatigue impact scale (FIS), EDSS subscores, 9-hole peg test (9-HPT), and SF-36 score (randomization to month 12).

Thirteen (12.6%) patients treated with MD1003 achieved clinical improvement in MS-related disability at month 9, confirmed at month 12, compared with none of the placebo-treated patients (p=0.0051). Most of the patients (10 out of 13) responded on the EDSS sub-score while 5 responded on the TW25 sub-score (2 patients responded on both). Results were similar for the primary endpoint on a per-protocol basis (N=129): 14.9% of patients in the intervention group responded and none in the control group (p=0.0093). The percentages of responders were 9.5% in the PPMS subgroup and 14.7% in the SPMS subgroup.

In the extension phase, the proportion of responders at M18 confirmed at M24 in the placebo/biotin group, i.e. the patients who were receiving their first biotin intakes, was 7.14%, i.e. slightly lower than the biotin group proportion of the responders at M6 confirmed at M9 that was 10.68%. The proportion of responders in the biotin-biotin sequence group was 13.19%, i.e. stable. At month 24 (end of the extension phase)14/91 (15.4%) patients initially treated with MD1003 and 5/42 (11.9%) patients initially treated with placebo had reduced MS-related disability.

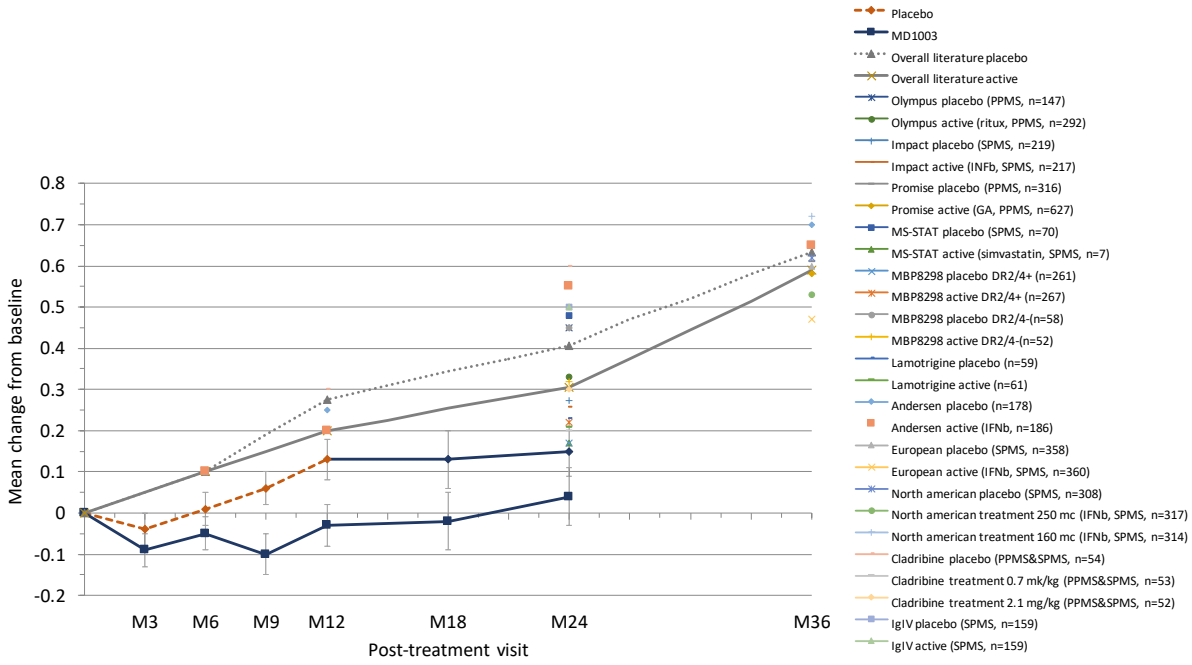
On the other hand, the proportion of patients with worsened EDSS scores (confirmed at two visits) increased at a faster rate in the placebo group compared to the biotin group: at M9 (confirmed at M12), it reached 13.64% and 4.21%, respectively. This result was not statistically significant (p=0.0727). At M18 (confirmed at M24), the proportion continued to increase in the biotin/biotin group, reaching 9.88%; the increase was also observed in the placebo/biotin group but at a faster rate, and reached 31.71%, this result was found statistically significant (p=0.0045) indicating that early treatment with biotin decreased the rate of disease's progression.

As a result, mean EDSS scores decreased during the study in the biotin group, but increased in the placebo group. The changes from baseline at M9 and at M12 were statistically different in the biotin group compared to the placebo group: p=0.0223 at M9 and p=0.0139 at M12. At M12, once the patients included in the placebo group had been switched to biotin for the extension phase, the increase of the mean EDSS change from baseline, that had been observed in the double-blind phase, stopped and remained constant until the M24 assessment (+0.13 at M12 versus +0.15 at M24). In the patients who had already been receiving biotin during the double-blind phase, the mean change EDSS (from baseline) remained relatively stable over 24 months (-0.03 at month 12 versus +0.04 at month 24). This indicates, that the 12-month delay in initiating active treatment in the placebo/biotin group resulted in a higher level of disability compared to the 24-month of active treatment administration in the biotin/biotin group.

Results of patient reported outcome measures also showed statistically significant differences in favor of the biotin group for the Clinician and Subject Global Impression of change Scales (CGI and SGI): the mean (SD) CGI was better in the biotin group compared to the placebo group: 4.05 (0.81) versus 4.62 (0.75), and this difference was statistically significant (p<0.0001). Similarly, the mean (SD) SGI was better in the biotin group compared to the placebo group: 4.27 (1.05) versus 4.76 (0.89), and this difference was statistically significant (p=0.0094). During the extension phase, the CGI and SGI were relatively stable in the biotin/biotin group between M12 and M24. In the placebo/biotin group, once the patients had switched to biotin, CGI and SGI improved. As a result, at M24, the mean CGI (SD) and SGI were identical in the biotin/biotin group and in the placebo/biotin group: 4.17(0.97) versus 4.21(0.75) for CGI (p=0.9270); and 4.47(1.07) versus 4.41(0.87) for SGI (p=0.7207).

Compared to previous trials in progressive MS, the effect size of MD1003 on mean EDSS progression is better than any drug tested so far in primary or secondary progressive MS (based on published data only):

Mean change EDSS in the MS-SPI in the context of previous published trials in PPMS and SPMS involving>6000 patients.



The incidence and distribution of adverse events (AEs) were similar in both study arms during the double-blind phase. Most (97%) AEs observed in the intervention group were of mild-or-moderate intensity. The only serious AE (SAE) reported in more than one patient was MS relapse observed in 4 (3.9%) patients in the intervention group and 4 (7.8%) patients in the control group. Three serious AEs were possibly related to MD1003: MS relapse, mucocutaneous rash, and hypoglycaemia in a diabetic patient treated with insulin. Allergic reaction, such as mucocutaneous rash, is a known side effect reported with medicines containing biotin and is considered as an identified risk with MD1003.

One patient died during the study: a suicide in a patient randomized to MD1003 that was considered as unrelated to treatment by the investigator.

Five cases of apparent biological hyperthyroidism were recorded as AEs, one of whom underwent thyroidectomy. Among these, 4 cases were without clinical symptoms and it was subsequently determined that they were due to abnormal thyroid function laboratory tests arising from biotin interference with the immunoassays using a biotinylated reagent. This results in falsely low values with sandwich immunoassays and false elevations with competitive immunoassays (Kwok *et al.*, 2012, Wijeratne *et al.*, 2012).

Brain MRI (T2 sequence) identified new MS lesions in 11 (23.4%) MD1003-treated and in 3 (13.0%) placebo-treated patients (p=0.356). Four MD1003-treated patients had enlarging lesions (0 [0%] in placebo-treated patients; p=0.3). Two patients had at least one post-gadolinium enhancing lesion on T1 sequence in the MD1003 group versus none in the placebo group (p=1.0).

In the extension phase, one case of myopathy with muscular lipidosis was reported in a patient after 6 months of treatment with MD1003. The patient recovered progressively. A causal relationship with the study drug is plausible considering that biotin by stimulating ACC should increase the levels of its end-product, malonyl-CoA. High levels of malonyl-CoA are known to inhibit carnitine palmitoyltransferase 1 (CPT1), which is responsible for long-chain fatty acid transport into mitochondria for further degradation, resulting in reduced fatty acid beta-oxidation (Foster, 2012, McGarry *et al.*, 1978). Consequently, it is theoretically possible that high doses of biotin could result in lipid storage myopathy under specific circumstances not identified in this single patient (CPT1 gene analysis did not reveal any mutation or polymorphism).

3) Randomized, double-blind, placebo-controlled trial in adult patients suffering from chronic visual loss after optic neuritis related to multiple sclerosis (MS-ON)

This study was intended to demonstrate the effects of high doses of biotin in MS patients with permanent visual loss following optic neuritis (ON).

Study population: Eligible patients were 18 to 75 years of age with MS that fulfilled revised International Panel criteria (Polman *et al.*, 2011) and unilateral or bilateral optic neuropathy with a visual acuity (VA) of the worst (diseased) eye ≤5/10 confirmed at 6 months. (Early Treatment Diabetic Retinopathy Study (ETDRS) score ≤ 72). All patients had evidence of visual acuity worsening in the last three years either following an optic neuritis relapse or in the context of chronic progressive optic neuritis. Patients with an optic neuritis relapse in the 6 months prior to inclusion were excluded.

Study design: This was a 6-month double-blind, 2:1 randomized, placebo-controlled trial that compared MD1003 (biotin 300 mg/day) with placebo. Treatment duration was 24 weeks followed by a pre-planned extension phase where the placebo was switched to the active. Biotin was administered orally at a dose of 100 mg thrice daily (morning, noon, evening). All usual patient treatments were allowed throughout the study, including immunomodulatory and immunosuppressive drugs providing these therapies were initiated ≥3 months before inclusion (≥1 month for fampridine). Intravenous methylprednisolone without oral taper was allowed upon MS relapse.

Assessments and endpoints: The primary endpoint was the mean change in best corrected visual acuity (logMAR) at 100% contrast between baseline and month 6 of the diseased eye (where the diseased eye is defined as the eye with the worst visual acuity (<5/10) at baseline and with evidence of worsening during the past three years).

Secondary endpoints were the proportion of patients with improvement of VA of the diseased eye of at least 0.3 logMAR; the proportion of patients with improvement of bilateral VA from <5 to ≥5/10 at 100% contrast; the proportion of eyes with reappearance of P100 waves or improvement of P100 latencies≥10 ms at M6 (or M12 for the extension phase); the clinical global impression at M6 and M12 evaluated by the clinician (CGI) and by the patient (SGI); the mean change in NEIFVQ-25 (functional vision questionnaire) between baseline and M6 (or M12 for the extension phase); and the mean change in SF36 between baseline and M6 (or M12 for the extension phase).

Safety was investigated by comparing the incidence of AEs and laboratory/ electrocardiography (ECG) findings between study arms.

Statistical analysis: We compared differences in mean absolute change in VA using analysis of covariance (ANCOVA) with a 0.05 two-sided significance level with adjustment on baseline values.

Baseline patient demographic characteristics were generally well balanced between study arms, regarding age, sex, age of onset, and duration of the disease. Patients either suffered from visual loss following an optic neuritis relapse (ON relapses, n=62) or from chronic progressive optic neuritis (progressive ON, n=31). A greater proportion of patients with progressive ON were attributed to the active arm (37%) as compared to the placebo arm (25%).

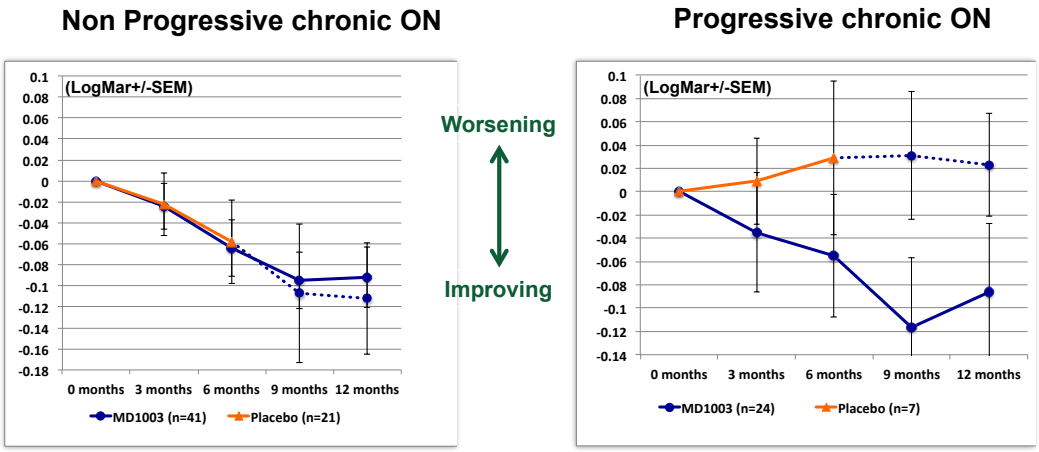
Primary endpoint:

Overall, there was no significant difference in the mean change of visual acuity amongst treatment groups (p=0.6581).

Prospectively defined subgroup analyses identified that only patients with progressive ON might have benefited from MD1003 while no effect was observed in the largest subgroup of patients with non-progressive ON following a relapse:

- In the subgroup of patients with progressive ON, 100% contrast VA of the diseased eye improved by a mean of 3 letters in the active arm *versus* worsening by 1.5 letters in the placebo arm. The evolution of other important endpoints was consistent with the improvement of 100% contrast VA.

- MD1003 had no effect at all in the subgroup of patients with non-progressive ON subsequent to a relapse: the 100% contrast visual acuity improved by 3 letters in both active and placebo arms.



Pre-planned subgroup analyses of the MS-ON trial. After 6 months, patients having received the placebo were switched to the active drug for 6 months. The data suggest that MD1003 is able to reverse progression in patients with progressive visual loss (right panel). In contrast no effect is detected in the subgroup of patients with non-progressive visual loss following a relapse (optic neuritis sequelae, left panel).

Biotin was well tolerated, with a similar safety profile to placebo. No drug related safety issues were identified confirming the limited risk of exposure to MD1003. During the double-blind phase of the study, 9 patients (13.8%) in the MD1003 group experienced a MS relapse versus 1 patient (3.6%) in the placebo group.

Overall, results of the open label and double-blind phases of MS-SPI and MS-ON studies showed a beneficial effect of high-dose biotin in patients with progressive MS. The SPI2 study is anticipated to confirm these results in a larger international trial.

1 STUDY OBJECTIVES

1.1 Primary objective

The primary objective of the SPI2 study is to confirm the superiority of MD1003 at 300 mg/day over placebo to clinically improve patients with not active progressive MS.

1.1.1 Primary endpoint

The primary endpoint is a composite criterion which can be met in one of two ways: either through confirmed improvement in the EDSS score or in TW25.

The composite criterion includes either

- a decreased EDSS at M12 confirmed at M15 (decrease of at least 1 point if baseline EDSS is from 3.5 to 5.5 and of at least 0.5 point if baseline EDSS is from 6 to 6.5) compared to baseline EDSS

or

- an improved TW25 of at least 20% at M12 confirmed at M15 compared to baseline TW25.

The baseline score for EDSS will be the lowest (best) value obtained during either the inclusion or randomization visits. For the TW25, the baseline value will be the best mean of the 2 values obtained at either the inclusion or randomization visits (the lowest mean value between these 2 visits).

The TW25 value at visit M12 is defined as the mean of the two TW25 attempts at visit M12. The TW25 value at visit M15 is defined as the mean of the two TW25 attempts at visit M15.

1.1.2 Primary efficacy measure

The primary efficacy measure is the comparison of the proportion of patients achieving either composite criterion at M12 confirmed at M15 across treatment groups.

1.2 **Secondary objectives**

1.2.1 Secondary efficacy endpoints

Secondary endpoints will be assessed at the end of the placebo-controlled phase. Secondary endpoints are listed hierarchically:

1. Time to EDSS progression confirmed at 12 weeks;
2. Mean difference between treatment arms in CGI at M15;
3. Mean difference between treatment arms in SGI at M15;
4. Mean change in TW25 score between M0 and M15;
5. Mean change in TW25 score between M0 and the last visit in double-blind phase of any particular patient (M15, M18, M21, M24 or M27 or Early Termination).

1.2.2 Exploratory endpoints

1. Brain MRI measurements will assess the following endpoints between M0 and M15 (and between M0 and M27 and every year until the end of the study):
    a. Percent whole brain volume change
    b. Percent thalamic volume change
    c. Percent cortical grey matter volume change
    d. Brain water content by Pseudo T2 relaxation time change
    e. NAA/Cr in a subset of sites acquiring MRS
2. Remote monitoring of ambulatory activity between M0 and M15 (and between M0 and M27 and every year until the end of the study)
3. Mean change in the Multiple Sclerosis Quality of Life-54 (MSQOL54) and Caregiver health-related quality of life in Multiple Sclerosis (CAREQOL-MS) subscores and composite scores between M0 and M15 (and between M0 and M27 and every year until the end of the study)
4. Mean change in subscores of the Kurtzke functional score between M0 and M15 (and between M0 and M27 and every year until the end of the study)
5. Mean change in Symbol Digit Modalities Test (SDMT) between M0 and M15 (and between M0 and M27)

1.2.3 Safety of MD1003

Safety of MD1003 will be assessed by:

1. Recording of AEs at each visit
2. Laboratory testing (standard haematology and biochemistry panel) including:

a. CBC with differential:
    i. Number and types of white blood cells (WBCs)
    ii. Number of red blood cells (RBCs)
    iii. Red cell distribution width (RDW)
    iv. Haematocrit
    v. Haemoglobin
    vi. Mean corpuscular volume (MCV)
    vii. Mean corpuscular haemoglobin
    viii. Platelet count
b. Metabolic panel (fasting):
    i. BUN
    ii. CO2 (carbon dioxide/bicarbonate)
    iii. Creatinine, estimated creatinine clearance rate using Cockcroft-Gault formula
    iv. Glucose
    v. Serum chloride
    vi. Serum potassium
    vii. Serum sodium
c. Hepatic function panel:
    i. Aspartate transaminase (AST)
    ii. Alanine transaminase (ALT)
    iii. Bilirubin
    iv. Gamma-glutamyl transpeptidase (GGT)
    v. Alkaline phosphatase
d. Lipid panel (fasting)
    i. Total cholesterol
    ii. Triglycerides
    iii. HDL cholesterol
    iv. LDL cholesterol
e. Thyroid panel
    i. Thyroid-stimulating hormone (TSH)
    ii. Free triiodothyronine (T3 free)

3. ECG at M0, M15, M27, M42, M54, and M66: PR, QRS, QT and RR interval, HR and QTcF, wave morphology, rhythm and conduction
4. Brain MRI at M0, M6, M15, M27, M42, M54, and M66:
    a. Comparison of proportion of patients with at least one new/enlarging T2-weighted MS lesion at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
    b. Comparison of proportion of patients with at least one gadolinium enhancing lesion on the T1-weighted sequence at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
    c. Mean number of gadolinium enhancing lesions on the T1-weighted sequence at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
    d. Mean number of new enlarging T2-weighted lesions per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
    e. Mean of T2-weighted lesion volume per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
    f. Mean of non-enhancing T1-weighted lesion volume per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
5. C-SSRS score: Suicidal ideation and behavior will be assessed during this trial at each visit using the suicide behavior questionnaire Columbia-Suicide Severity Rating Scale.

2 INVESTIGATIONAL PLAN

2.1 Overall study design

PART 1:

The duration of Part 1 is 27 months. The randomized double-blind placebo-controlled period ranges from 15 to 27 months depending upon the randomization date of an individual patient.

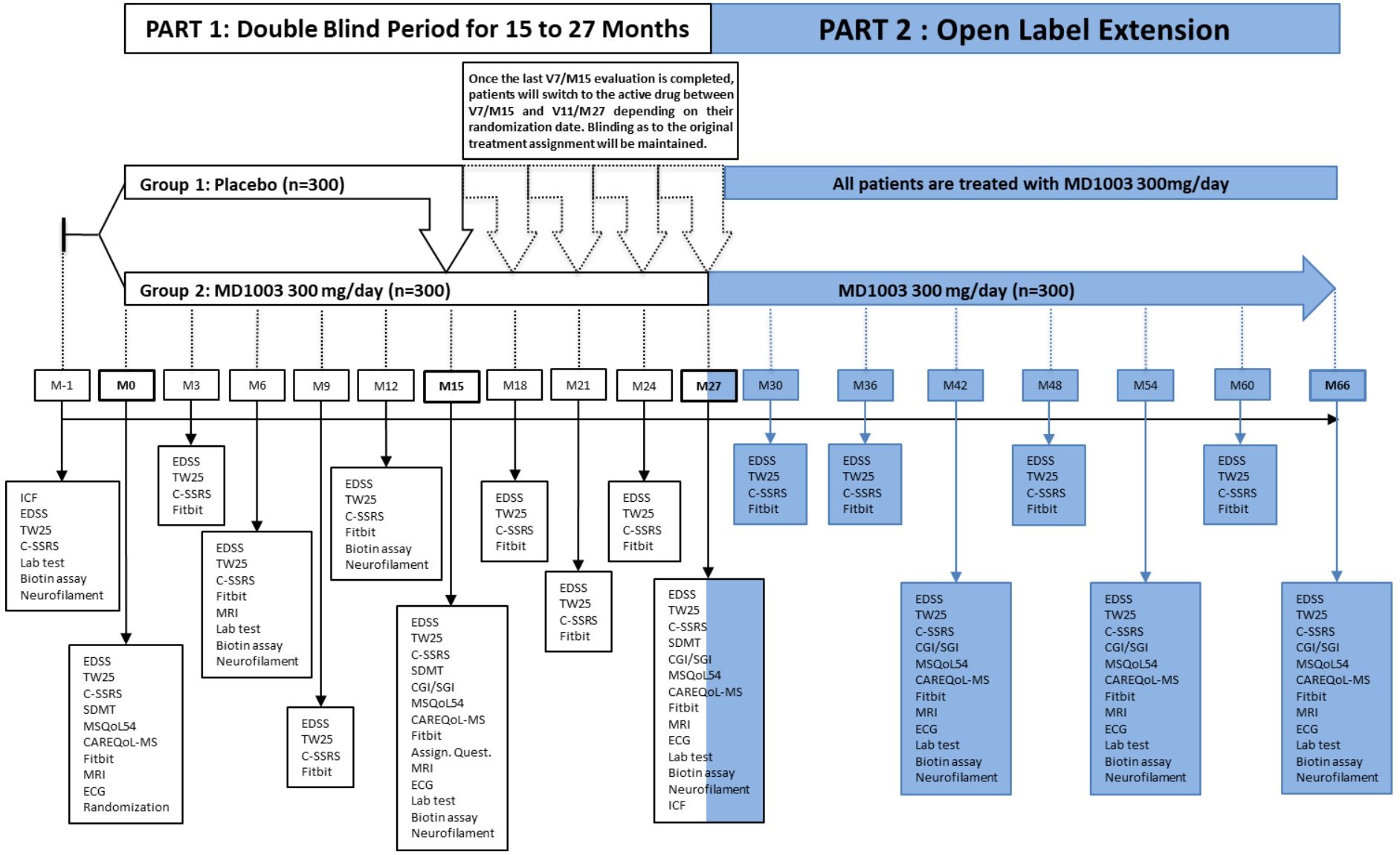
Once the last month 15 evaluation of the study has been completed, patients will switch to the active treatment at the next planned visit. Patients and study personnel will remain blinded as to the original treatment arm until the last V11/M27 visit of the study has been completed.

PART 2:

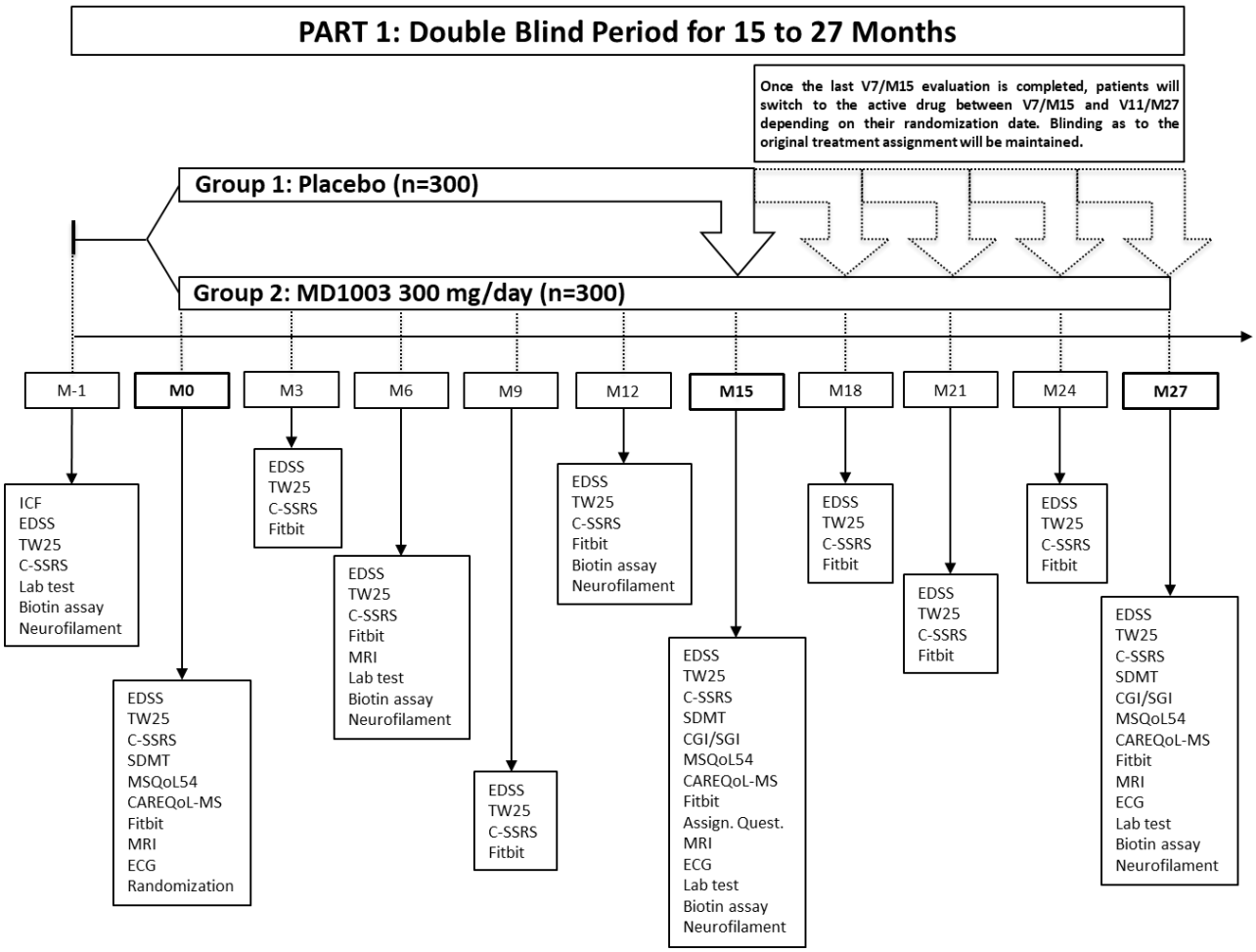
At the last evaluation of Part 1 (Visit 11/Month 27) all participants will be offered active treatment in an open label extension for 39 additional months (From V11/M27 to V18/M66).

The purpose of the active drug extension is to further define the safety of MD1003.

The total duration of the study (Part 1 + Part 2) is 66 months. If the study fails to meet the primary outcome measure or is terminated by either the Sponsor or upon DSMB recommendation, then all patients in both Part 1 and Part 2 will undergo an Early Termination Visit (see section 2.6.3.4) as soon as practicable and the study drug discontinued.


PART 1: Double Blind Period for 15 to 27 Months
PART 2 : Open Label Extension
Once the last V7/M15 evaluation is completed, patients will switch to the active drug between V7/M15 and V11/M27 depending on their randomization date. Blinding as to the original treatment assignment will be maintained.
Group 1: Placebo (n=300)
All patients are treated with MD1003 300mg/day
Group 2: MD1003 300 mg/day (n=300)
MD1003 300 mg/day (n=300)
M-1
M0
M3
M6
M9
M12
M15
M18
M21
M24
M27
M30
M36
M42
M48
M54
M60
M66
ICF
EDSS
TW25
C-SSRS
Lab test
Biotin assay
Neurofilament
Randomization
Fitbit
MRI
SDMT
MSQoL54
CAREQoL-MS
CGI/SGI
Assign. Quest.
ECG

2.1.1 **PART 1**: Randomized double-blind placebo-controlled period for 15 to 27 months



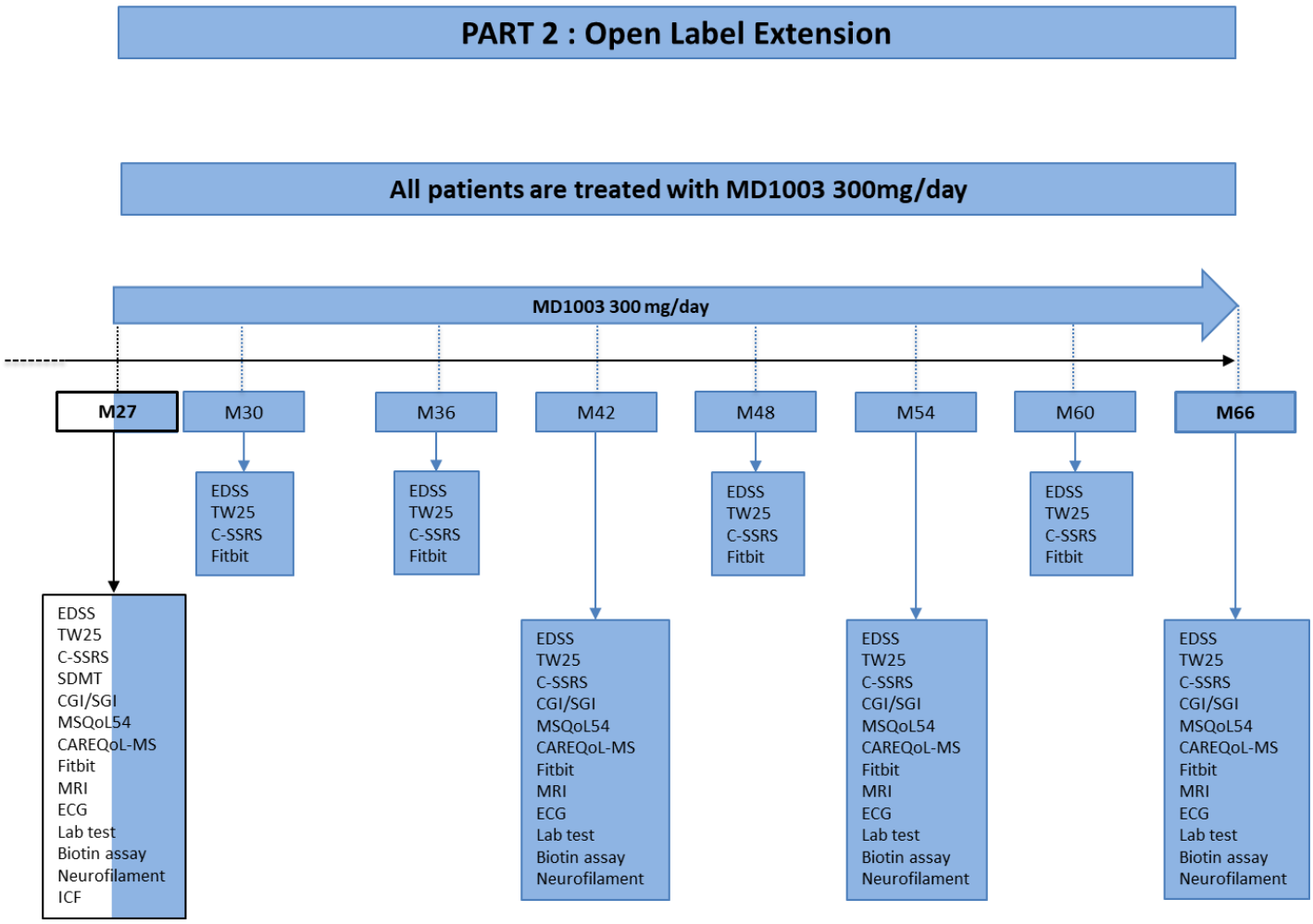
Part 1 is a randomized double-blind placebo-controlled period for 15 to 27 months. The blinded placebo-controlled phase will last for at least 15 months but no longer than 27 months and will end when the last month 15 evaluation for the last-enrolled study subject has been completed.

Patients who complete 15 months will be maintained on their original treatment assignment (MD1003 versus placebo) for a maximum of 27 months or until the last Month 15 evaluation of the study is completed, whichever comes first. Patients and study personnel will remain blinded as to the original treatment assignment.

Once the last month 15 evaluation for all study subjects has been completed, patients will switch to the active drug at the next planned study visit (V8/M18 or V9/M21 or V10/M24 depending on their randomization date). Patients will remain blinded to their original treatment arm until the last V11/M27 visit of the study has been completed.

Maximum study duration per patient for Part 1 will be no longer than 27 months.

2.1.2 **PART 2**: Open Label Extension (39 months)



Part 2 is an open label extension for 39 months. All patients who completed 27 months (V11/M27) will be offered active treatment in an open label extension from V11/M27 to V18/M66.

The maximum study duration per patient for Part 1 and Part 2 will be no longer than 66 months (27 + 39 months).

2.2 Number of patients

The study will include approximately 600 patients at 90 centers located in North America, Australia and Europe divided into 2 groups:

- Group 1 (300 patients): placebo, three times a day
- Group 2 (300 patients): MD1003, 300 mg/day given as 100 mg three times a day.

2.3 Selection and withdrawal of patients

2.3.1 Inclusion criteria

1. Patient aged 18-65 years old
2. Signed and dated written informed consent form in accordance with local regulations: having freely given their written informed consent to participate in the study

3. Diagnosis of primary or secondary progressive MS fulfilling revised McDonald criteria (2010) and Lublin criteria (2014)

4. Documented evidence of clinical disability progression within the 2 years prior to inclusion, i.e. a) progression of EDSS during the past two years of at least 1 point sustained for at least 6 months if inclusion EDSS is from 3.5 to 5.5 or at least 0.5 point increase sustained for at least 6 months if inclusion EDSS is from 6 to 6.5 or b) increase of TW25 by at least 20% in the past two years sustained for at least 6 months or c) other well-documented objective worsening validated by the Adjudication Committee

5. EDSS score 3.5 to 6.5 at inclusion defined as follows:

   3.5: Fully ambulatory but with moderate disability in one functional system (one FS grade 3) and mild disability in one or two FS (one / two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1); or fully ambulatory with five FS grade 2 (others 0 or 1)

   4.0: Ambulatory without aid or rest for > 500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps

   4.5: Ambulatory without aid or rest for > 300 meters; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps

   5.0: Ambulatory without aid or rest for > 200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)

   5.5: Ambulatory without aid or rest for >100 meters

   6.0: Unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting

   6.5: Constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting

   Within the 4.5 to 6.5 range, the EDSS relies mainly on the Ambulatory Score:

   2: ≥300 meters, but <500 meters, without help or assistance (EDSS 4.5)

   3: ≥200 meters, but <300 meters, without help or assistance (EDSS 5.0)

   4: ≥100 meters, but <200 meters, without help or assistance (EDSS 5.5)

   5: Walking range <100 meters without assistance (EDSS 6.0)

   6: Unilateral assistance, ≥50 meters (EDSS 6.0)

   7: Bilateral assistance, ≥120 meters (EDSS 6.0)

   8: Unilateral assistance, <50 meters (EDSS 6.5)

   9: Bilateral assistance, ≥5 meters, but <120 meters (EDSS 6.5)

6. TW25<40 seconds at inclusion visit

7. Kurtzke pyramidal functional subscore ≥2 defined as “minimal disability: patient complains of motor-fatigability or reduced performance in strenuous motor tasks” (motor performance grade 1) and/or BMRC grade 4 in one or two muscle groups”

2.3.2 Exclusion criteria

1. Clinical evidence of a relapse in 24 months prior to inclusion
2. Treatment with any product containing biotin as single ingredient within six months prior to inclusion (multivitamin supplementation authorized if biotin < 1mg per day)
3. Concomitant treatment with fampridine at inclusion or in the 30 days prior to inclusion
4. New immunosuppressive/immunomodulatory drug initiated less than 90 days prior to inclusion
5. Treatment with botulinum toxin (except for cosmetic purposes) initiated within 6 months prior to inclusion
6. In-patient rehabilitation program within the 3 months prior to inclusion
7. Pregnancy, breastfeeding or women with childbearing potential without acceptable form of contraception
8. Men unwilling to use an acceptable contraceptive method
9. Any general chronic handicapping/incapacitating disease other than MS
10. Any serious disease necessitating biological follow up with biological tests using biotinylated antibodies or substrates
11. Past history of rhabdomyolysis/metabolic myopathy
12. Known fatty acids beta oxidation defect
13. Known hypersensitivity or intolerance to biotin, analogues or excipients, patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption
14. Patients with hypersensitivity or contra-indication to gadolinium
15. Patients with uncontrolled hepatic disorder, renal or cardiovascular disease, or cancer
16. Laboratory tests out of normal ranges considered by the investigator as clinically significant with regards to the study continuation
17. Patients with history or presence of alcohol abuse or drug addiction
18. Untreated or uncontrolled psychiatric disorders, especially suicidal risk assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)
19. Participation in another research study involving an investigational product (IP) in the 90 days preceding inclusion, or planned use during the study duration
20. Patients likely to be non-compliant to the study procedures or for whom a long-term follow-up seems to be difficult to achieve
21. Relapse that occurs between inclusion and randomization visit

2.3.3 Contraception

Both male and female patients who are not either surgically sterile (tubal ligation/obstruction or removal of ovaries or uterus) or post-menopausal (no spontaneous menstrual periods for at least one year confirmed by a negative hormone panel) must commit to using one highly effective method (such as

intrauterine device, sterilisation of one of the partners, hormonal birth control methods) plus one supplementary barrier method (such as condom, diaphragm) with a spermicide for the duration of the study and for two months after the treatment termination (or 90 days according to local regulations).

Birth control methods which are considered as highly effective (low failure rate less than 1% per year) when used consistently and correctly include:

- Established use of oral, injected or implanted hormonal methods of contraception;
- Placement of an intrauterine device or intrauterine system;
- Female bilateral tubal ligation;
- Vasectomized partner;
- Sexual abstinence: When this is in line with the preferred and usual lifestyle of the patient. Note: Periodic abstinence (e.g. calendar ovulation, thermal, post-ovulation methods) and withdrawal are not highly effective methods of contraception.

Supplementary barrier methods of birth control include:

- Male or female condom with spermicidal foam/gel/film/cream/suppository;
- Cap, diaphragm or sponge with spermicidal foam/gel/film/cream/suppository.

Pregnancy testing: For women of childbearing potential, a highly sensitive serum HCG test will be added to the biological safety panels, and the patient will be asked to perform a monthly urinary test during the study and for up to three months after study termination, using kits provided by the sponsor.

2.3.4 Follow up of pregnancy

A female subject must immediately inform the investigator if she becomes pregnant during the study and discontinues the study treatment. The investigator should report all pregnancies to the sponsor on the form provided. Monitoring of the subject should continue until the conclusion of the pregnancy and until 3 months after the birth of the baby following local regulation.

If the female pregnant partner of the male subject agrees to provide information regarding her pregnancy, she will be asked to sign the pregnant partner consent form template. In addition, the following information will be collected from the pregnant partner: relevant medical history, details of any previous pregnancies including outcome and any complications, details about the current pregnancy, any drugs taken during your pregnancy, the outcome of the pregnancy, details of the birth and delivery, details about the health of the baby until 3 months after the birth. This information will only be collected in the event that the female partner of a male subject participating in this study becomes pregnant during the male subject's participation in this study.

2.3.5 Patient identification and assignment of patient number

Patients will be numbered sequentially. Each patient in the study must be assigned a unique subject number and must keep that number throughout the study even if he or she transfers to another site. A patient who is included but not randomized may be re-screened at a later time, only upon sponsor validation. An inclusion number must never be reassigned for any reason. The investigator must maintain a patient master log linking the patient number to the patient's name. The investigator must follow all applicable privacy laws in order to protect a patient's privacy and confidentiality. Information that could identify a patient will be masked on material received by the sponsor.

The allocation of patient number will be done through the EDC using the Interactive Web Response System (IWRS) at the first visit (V1/Inclusion visit) in chronological order of signature of the informed consent form in the study. Once patient numbers are assigned, they cannot be reassigned.

2.3.6 Screening failures

Patients who sign an informed consent form but fail to meet the eligibility criteria are defined as screening failures. For all screening failures, the investigator is asked to maintain a screening log that documents the patient number, reason (s) for screening failure and justification for rescreening if applicable. A copy of this log should be retained in the investigator's study file. The demography, the eligibility and end of trial forms will be completed and returned to the sponsor for screening failures.

2.3.7 Premature discontinuation of treatment

The treatment may be prematurely and definitively discontinued for a participant for one of the following reasons:

- **Adverse event:** clinical or laboratory event that in the medical judgement of the investigator for the best interest of the patient are grounds for discontinuation
- **Occurrence of pregnancy**
- **Withdrawal of consent:** patient desires to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the investigator.
  The reason of consent withdrawal should be documented on the eCRF when available.
- **Suicidal risk evaluated by suicidal risk assessed by Columbia-Suicide Severity Rating Scale (C-SSRS)**

The investigator should record the primary reason and the date of the premature discontinuation of the treatment in the electronic case report form (eCRF).

In the event that a patient discontinues or is withdrawn from the treatment and/or from the study, the investigator will notify the sponsor and when possible the safety and efficacy determinations designated under the final visit will be obtained on the last day on which the patient receives the investigational product or as soon as possible thereafter.

2.3.7.1 Withdrawal from the treatment

Patients who discontinue study treatment for any reason will be encouraged by sites to remain on study for all remaining study evaluations and procedures according to regular visits schedule. Follow-up visits should continue for as long as possible with scheduled investigations at V6/M12 and V7/M15 for an ITT analysis.

2.3.7.2 Withdrawal from the study

Subjects who desire to withdraw from further participation in the study in the absence of a medical need will be asked to attend for an early termination visit where all protocol evaluations & procedures (or at least safety assessments) will be performed.

Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from the study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

2.3.7.3 Lost to Follow Up

In case a patient is lost to follow up every effort should be made to confirm that the patient has decided to withdraw his consent. At least three calls on different days and times should be performed with

leaving a voice message if possible. If attempts to contact the patient fail, a registered letter should be sent to the patient's residence. Depending on the country regulation, the investigator should contact the primary care physician/general practitioner to obtain any recent information on the patient.

All attempts to contact or obtain information on the patient should be documented in source documents.

2.3.8 Premature termination or suspension of the study

If the trial is terminated prematurely or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

- If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension. The investigator will coordinate with the sponsor to return all IP vials, and other study materials.
- If the sponsor terminates or suspends a trial, the investigator should promptly inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.
- If the IRB/IEC terminates or suspends its approval/favorable opinion of a trial, the investigator should inform the institution, where required by the applicable regulatory requirements, and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial/study reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s).

If the study fails to meet the primary outcome measure or is terminated by either the Sponsor or upon DSMB recommendation, then all patients in both Part 1 and Part 2 will undergo an Early Termination Visit (see section 2.6.3.4) as soon as practicable and the study drug discontinued.

2.4 **Investigational products, control therapies and administration**

Investigational products and control therapies will be administered only to patients who have provided informed consent.

2.4.1 Description of investigational product and control arm

2.4.1.1 Investigational products

Investigational products units will be supplied by the sponsor or designee.

- MD1003 capsules

The investigational product will consist in capsules of 100 mg MD1003 and excipients (lactose).

2.4.1.2 Control arm

- Placebo capsules

This formulation consists of lactose powder as placebo.

2.4.1.3 Dose regimen

The dose regimen will be 1 capsule three times a day (tid, one in the morning, one at noon, one in the evening) in a fasted state (before meal times) as a slight food effect has been established in pharmacokinetics studies. Capsules have to be swallowed with a glass of water with a minimum of 4 hours between each intake and at least one hour before mealtime.

- Group 1 (placebo): one placebo capsule tid
- Group 2 (MD1003, 300 mg/day): one capsule of MD1003 tid

2.4.1.4 Summary of known and potential risks and benefits, if any to human subjects

- Expected benefits

Preventing or reversing the development of pathology should reduce the severity of the clinical expression of the disease, especially with regard to motor performances, quality of life.
Benefit on the quality of life of relatives taking care of the patient is also expected.

- Potential risks

  - Teratogenicity

During the non-clinical development with MD1003, a risk for teratogenicity has been identified in a reproduction study in rabbits at doses corresponding to those used in humans. Therefore, correct contraception measures should be undertaken during treatment with MD1003 and in case of pregnancy, the treatment with MD1003 should be discontinued.

  - Intolerance to lactose

This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take MD1003.

  - Laboratory tests errors - Interference with immunoassays

Biotin may interfere with some assays used in clinical analyzers that are based on a biotin/streptavidin interaction leading to laboratory reporting errors. Therefore, special consideration must be given to patients requiring laboratory tests such as thyroid functions, pregnancy tests, and troponin, but erroneious results may also occur for a large number of tests used in the diagnosis and monitoring of cardiovascular, neoplastic, hemotologic, infectious, endocrine, bone and inflammatory diseases (See Section 3.1 for more details).

  - Hypoglycaemia in diabetic patients

In the clinical studies with MD1003, one patient with Type 1 diabetes who was receiving insulin experienced episodes of hypoglycaemia approximately 1 year after initiating MD1003. These ceased when MD1003 was stopped and recurred on re-challenge. A potential influence of MD1003 on the effect of insulin cannot be ruled out and the patient's dose of insulin may need to be adjusted.

  - Relapses

Across the double-blind placebo-controlled phases of the two clinical studies evaluating MD1003 in MS patients, a similar proportion of patients treated with MD1003 (6.5%) and placebo (6.2%) reported MS relapses in the progressive MS population whereas in the relapsing remitting MS population, the proportion was higher in the MD1003 group (13.3%) compared to the placebo group (7.1%). MD1003 is only being studied in non-relapsing progressive forms of MS.

- Dermatologic reactions

In the double-blind placebo-controlled phases of the clinical studies, the drug reactions of blister, eczema and mucocutaneous rash occurred in three different patients treated with MD1003, each event occurring in only 1 patient (0.6% for each drug reaction). No patients in the placebo group reported these events.

- Myopathy

In the open label extension phases of the previous studies, myopathy occurred in one patient (0.4%) 5 months after initiation of MD1003 from which he fully recovered when MD1003 was stopped. The investigations performed (electromyography and muscular lipidosis observed after muscle biopsy), indicated a lipid storage myopathy. A causal relationship with MD1003 cannot be ruled out as biotin could result in lipid storage myopathy by inhibiting the fatty acids beta-oxidation pathway.

2.4.2 Packaging and labelling

The sponsor or designee will prepare and ship IP to the study pharmacist or to the Principal Investigator where appropriate. Each IP vial will be labelled according to local regulation requirements. For all randomized patients, the treatment will be dispensed by the hospital pharmacy (where applicable) the quantity of vials needed to cover the period until the next visit.

The capsules will be supplied in vials containing 90 capsules each corresponding to one month of treatment. The same colour will be used for placebo and active drug bottles.

In addition to the legal requirements label, a label indicating the treatment number and the treatment period will be attached to each vial.

2.4.3 Treatment assignment

At M0, patients will be randomly assigned to receive either placebo (group 1) or active drug 300 mg/day (group 2) for at least 15 months and no longer than 27 months.

The blinded placebo-controlled phase will last for at least 15 months and no longer than 27 months and will end when the last month 15 evaluation for all study subjects has been completed.

Once the last month 15 evaluation has been completed, all patients will switch to the active drug at the next scheduled visit. Participants and study personnel will remain blinded as to the original treatment assignment even after switching to active treatment.

At the V11/M27 evaluation, an open label extension (patients under active drug) will be offered to participants for 39 additional months.

Dispensation of the correct treatment during the double-blind period (Part 1) and the open-label extension (Part 2) will be automatically programmed by IWRS.

2.4.4 Randomization and blinding

- Randomization

At randomization visit (V2/M0), all eligible patients will be randomized to one of the two treatment arms. The randomization will be done in 1:1 ratio stratified by geographical region, and by disease history (PPMS or SPMS).

The treatment numbers will be provided at each visit by an Interactive Web Response System (IWRS).

- Blinding

This study is a double-blind study. Each product, active or placebo, will be supplied in size one capsules having the same appearance.

The capsules will contain the same quantity of white powder, with the same appearance and taste (MD1003 has no taste).

Placebo capsules will thus contain 100 mg more lactose in replacement of MD1003.

Investigators have no contact with the biostatistician in charge of the randomization list.

The treating physician is distinct from the blinded rater. The latter has no information about biological results or any potential adverse events reported by the patient in connection with the treatment received.

The treating physician will be responsible amongst others for supervising the study drug administration, recording and treating AEs, monitoring safety assessments including laboratory parameters, and for the physical examination and all other assessments except EDSS and TW25. The blinded rater will be responsible for all EDSS and TW25 assessments including the one performed at inclusion visit (V1/M-1) and those performed at any unscheduled visits required because of new or changing symptoms potentially related to MS.

Throughout the study, the blinded rater will remain blind to the subject's treatment, laboratory data, adverse event profile, and any changes in the safety assessments. Both the treating physician and the subject will be informed of the importance of not discussing these issues with the blinded rater to prevent unblinding. The blinded rater should only communicate with the subjects on matters related to their neurological status and should remind the subjects at each visit not to discuss other matters related to their treatment with him/her. The blinded rater should not have access to the eCRF, except for the EDSS and TW25 pages, and restricted access to the patient's files/reports.

Every effort must be made to minimize the communication between the blinded rater and the treating physician and Study Coordinators.

A special agreement for respecting the blinding procedure must be signed by all personnel involved in this study prior to the initiation of the study. The Sponsor will provide the blinding agreement.

The treating physician and the blinded rater will not have access to measures of MD1003 in blood at V4/M6, V6/M12, V7/M15 and V11/M27.

The treating physician and the blinded rater as well as patients will have no access to the randomization list until the end of the study, once the last 27-month evaluation of the study has been completed. This ensures that patients and physicians and raters will remain double-blinded during the study regarding whether a patient would have received the active or the placebo during the initial placebo-controlled phase of the study.

The investigator should ensure that the code is broken only in case of emergency with, if possible, prior contact to sponsor to explain why the unblinding is necessary. The investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the IP.

In order to control potential exposure to biotin prior to inclusion and during the study for patients of the placebo group, biotin serum level and its two main metabolites: bisnorbiotin (BNB) and biotin sulfoxide (BSO) will be measured in all patients at inclusion, V4/M6, V6/M12, V7/M15 and V11/M27. The samples will be collected and transferred all along the study to an independent laboratory (Atlanbio, France), where analyses will be performed blindly, under control of the Central Clinical Laboratory. Results of these analyses will not be disclosed to any participant prior to data base locking.

2.4.5 Investigational product shipping, handling and storage

IP will be shipped directly to the pharmacist (if applicable) designated by the Investigator after required regulatory and legal documents have been received by the sponsor or designee.

Upon receipt of the investigation products shipment, the pharmacist or the principal investigator will verify the condition and quantity of the study supplies, including inspection of document per instructions in the Pharmacy Binder. Room temperature during shipment (ie. +59°F to +77°F (+15°C to +25°C) for this study will be required.

The sealed Investigational Product (IP) bottles must not be opened until they are used for administration. Once unpacked and inspected, IP or control arm must be stored at room temperature, ie. +59°F to +77°F (+15°C to +25°C). The pharmacist must store the sealed investigation products in a secured area with access restricted to authorized personnel only. The IP must be stored as indicated.

Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor or designee. Once a deviation is identified, the IP must be quarantined and not used until the sponsor provides documentation of permission to use the IP.

Once the IP has been allocated and dispensed to the patient, it must be maintained at room temperature, i.e. +59°F to +77°F (+15°C to +25°C). The details on how to manage IP at site will be also provided in a separate drug manual (Investigator Manual CTS).

IP shipment to patient homes should be avoided as much as possible and should remain exceptional. Sponsor written approval is required and shipment can occur only under the following conditions:

- Evidence of what was packed for the subject
- Quality Control of the content of the shipment
- Delivery signature receipt
- Adequate and qualified couriers should be used (temperature tracker)
- Information letter should accompany the shipment
- Investigator must contact the patient to check good treatment receipt
- Investigator must check that the posology of the treatment is clearly understood
- All of the above must be documented in the medical file of the patient

2.4.6 Treatments compliance, accountability and return of therapeutic units

Regulatory agencies require accounting for the disposition of all IP received by each clinical site. Information on drug disposition required by law consists of the date received; date dispensed, quantity dispensed, and the patient to whom the drug was allocated and dispensed. The investigator is responsible for the accounting for all unused IP and all used IP containers through the pharmacist if applicable. The pharmacist or the principal investigator uses this information to maintain an accurate and complete dispensing and inventory record supplied by the sponsor or designee. At the completion or termination of the study, a final drug accountability review and reconciliation must be completed; any discrepancies must be investigated, and their resolution documented.

All unused IP must be returned to the sponsor/contract distribution center with the appropriate form.

IP will be dispensed by the pharmacy where applicable and the date of the dispensation will be documented in the patient's record in addition to the eCRF.

The remaining study medication will be checked at each visit by the investigator and the pharmacist before completing the drug dispensation records.

The remaining study medication, labels and dispensing records will be checked by the monitor to verify accurate dose dispensing.

2.4.7 Overdose

The Sponsor has established specific rules regarding compliance and management compliance deviation. Please find below the compliance ranges defined:

- Compliance <70%: it is considered as major deviation to the protocol
- Compliance between [70%; 80% [: it is considered as minor deviation to the protocol
- Compliance between [120%; 130]: it is considered as minor deviation to the protocol
- Compliance > 130%: it is considered as major deviation and an adverse event "overdosing" should be reported. See section 4. Adverse event for more information.

2.4.8 Destruction

Remaining study medication and packaging of used and non-used IP will be returned to the sponsor or its designee for destruction.

Recording of destruction operations should be carried out in such a manner that all operations may be accounted for. The records will be kept by the sponsor. This destruction will be done only after the finalization of the clinical trial and the compilation of the final study report, only upon approval of the Sponsor.

2.5 **Concomitant treatments**

Concomitant treatment is defined as any medication or physical therapy that is ongoing at inclusion or started during the trial.

2.5.1 Concomitant medication

For this study, concomitant medication is defined as any medication that is taken at the same time as the first administration of IP and will be recorded on the concomitant medication page of eCRF.

All usual treatments of the patient are authorized for the duration of the study, such as immuno-modulators, and immunosuppressive drugs including monthly pulses of IV methylprednisolone for patients already treated by these drugs. All of these drugs have to be initiated at least 3 months prior to inclusion and maintained at the same dose as much as possible, except IV methylprednisolone which may be used for relapses.

During the study, initiation or change of any of these drugs or DMT is not allowed, **but this is not a reason to withdraw a patient.** In case initiation or change of DMT is decided by the investigator, the following should be respected:

- Document accordingly, in source documents and eCRF
- Report as a protocol deviation
- Make every effort to keep patients in the study at least until the V7/M15 visit
- Continue or discontinue MD1003 should be discussed with Medical Monitors and Sponsor CMO

Intravenous methylprednisolone is authorized during the trial in case of MS relapse, without oral taper. Follow up visits must be scheduled before infusions.

As far as possible, visits have to be scheduled before steroids infusions rather than after.

All medications will be recorded in the eCRF and the patient's source documents.

2.5.2 Physical therapy

If the patient has previously followed a continuous physical therapy program at least 3 months prior to inclusion, this program should be maintained throughout the duration of the study and should not be discontinued. Intensive new in-patient rehabilitation therapy program is not allowed within the 3 months prior to inclusion and during the trial since it could impact EDSS assessments.

2.6 Visits schedule and evaluations

2.6.1 Study flow chart Part 1: double-blind period for 15 to 27 months

	M-1	**M0**	M3	M6	M9	M12	**M15**	M18	M21	M24	**M27**	Unscheduled Visits	Early Termination Visit
	Inclusion visit V1	**Randomization visit V2**	Follow-up visit V3	Follow-up visit V4	Follow-up visit V5	Follow-up visit V6	**Follow up visit V7**	Follow up visit V8	Follow up visit V9	Follow up visit V10	**Final double-blind visit V11**		
STUDY WINDOWS***	+/- 15 days		+/-10 days	+/- 10 days	+/- 10 days	+/- 10 days	+/- 15 days	+/- 15 days	+/- 15 days	+/- 15 days	+/- 15 days		
Informed consent	X										X		
Inclusion criteria	X	X											
Exclusion criteria	X	X											
Randomization		X											
Demographic Data	X												
Clinical examination*	X	X	X	X	X	X	X	X	X	X	X	X	X
EDSS	X	X	X	X	X	X	X	X	X	X	X	X	X
TW25	X	X	X	X	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X
Ambulatory activity monitoring		X	X	X	X	X	X	X	X	X	X	X	X
MS relapse questionnaire		X	X	X	X	X	X	X	X	X	X	X	X
SDMT		X					X				X		X
CGI-I (SGI & CGI)							X				X		X
MSQOL54 / CAREQOL-MS		X					X				X		X
Laboratory testing**	X			X			X				X	X	X
Blood-based pregnancy test[a]	X			X			X				X	X	X
Biotin blood level	X			X		X	X				X		X
Neurofilament blood level	X			X		X	X				X		X
ECG		X[b]					X				X	X	X
Brain MRI		X		X			X				X	X[c]	
Concomitant medication / therapies	X	X	X	X	X	X	X	X	X	X	X	X	X
Study medication dispensation		X	X	X	X	X	X	X	X	X			
Patient alert card dispensation	X	X	X	X	X	X	X	X	X	X	X	X	X
Compliance check			X	X	X	X	X	X	X	X	X	X	X
AEs reporting		X	X	X	X	X	X	X	X	X	X	X	X
Treatment assignment questionnaire							X						X

a: for women of childbearing potential; in addition, a urinary pregnancy test will be performed each month during the study and for 3 months after termination
b: triplicated ECG
c: in case of relapse
*: physical examination and vital signs / **: CBC with differential, Metabolic panel (fasting), Hepatic function panel and Lipid panel (fasting) / *** One month is equal to 28 days.

2.6.2 Study flow chart Part 2: Open label extension

	M30	M36	M42	M48	M54	M60	**M66**	Unscheduled Visits	Early Termination Visit
	Follow-up visit V12	Follow-up visit V13	Follow-up visit V14	Follow-up visit V15	Follow-up visit V16	Follow-up visit V17	**Final OLE visit V18**		
STUDY WINDOWS***	+/-15 days	+/- 15 days	+/- 15 days	+/- 15 days	+/- 15 days	+/- 15 days	+/- 15 days		
Informed consent									
Inclusion criteria									
Exclusion criteria									
Randomization									
Demographic Data									
Clinical examination*	X	X	X	X	X	X	X	X	X
EDSS	X	X	X	X	X	X	X	X	X
TW25	X	X	X	X	X	X	X	X	X
C-SSRS	X	X	X	X	X	X	X	X	X
Ambulatory activity monitoring	X	X	X	X	X	X	X	X	X
MS relapse questionnaire	X	X	X	X	X	X	X	X	X
SDMT									X
CGI-I (SGI & CGI)			X		X		X		X
MSQOL54 / CAREQOL-MS			X		X		X		X
Laboratory testing**			X		X		X	X	X
Blood-based pregnancy test[a]			X		X		X	X	X
Biotin blood level			X		X		X		X
Neurofilament blood level			X		X		X		X
ECG			X		X		X	X	X
Brain MRI			X		X		X	X[c]	
Concomitant medication / therapies	X	X	X	X	X	X	X	X	X
Study medication dispensation	X	X	X	X	X	X	X		
Patient alert card dispensation	X	X	X	X	X	X	X	X	X
Compliance check	X	X	X	X	X	X	X	X	X
AEs reporting	X	X	X	X	X	X	X	X	X
Treatment assignment questionnaire									

a: for women of childbearing potential; in addition, a urinary pregnancy test will be performed each month during the study and for 3 months after termination
b: triplicated ECG
c: in case of relapse
*: physical examination and vital signs / **: CBC with differential, Metabolic panel (fasting), Hepatic function panel and Lipid panel (fasting) / *** One month is equal to 28 days.

2.6.3 Evaluations

The **treating physician** will be responsible for collecting the following information: informed consent and background information, concomitant therapies, any adverse event, current medical status, laboratory testing results, ECG interpretation, inclusion/exclusion criteria, SDMT, MSQOL-54, CAREQOL-MS, CGI-I (both clinician and subject), C-SSRS, and end of randomized period treatment assignment questionnaire.

A blinded rater, independently from the treating physician, will perform the following evaluations: Neurostatus EDSS and/or TW25. The blinded rater for the EDSS and/or for TW25 is not necessarily a physician: the investigator may delegate the responsibility of the blinded rater to an individual qualified by training and experience, such as a nurse practitioner (NP) or a physician assistant (PA – applicable in USA). A blinded rater performing EDSS must be Neurostatus level C certified.

A separate central core lab different from treating physicians & blinded raters will perform the MRI and ECG analyses.

As far as possible, visits have to be scheduled before steroids infusions rather than after.

2.6.3.1 Evaluations Part 1: Double-blind phase for 15 to 27 months

2.6.3.1.1 Visit 1 (M-1): Inclusion visit

During the inclusion visit, the investigator will check inclusion/exclusion criteria and, after having obtained informed consent for study participation, will record the following information into the eCRF:

- Informed consent
- Medical history: major illnesses, previous surgery/operation and allergies
- Multiple Sclerosis history with Pattern of Progression
- Concomitant therapies recording including usual dose regimen of studied disease therapy
- Clinical examination including vital signs
- Demographic data (including racial/ethnicity data according to local regulations)
- Check inclusion criteria
- Check non-inclusion criteria
- EDSS
- TW25
- C-SSRS
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will organize blood sampling and transfer to the Central Clinical Laboratory of the safety panel following the Operating Manual, the results to be available for the inclusion:

- Safety panel includes:
    - CBC with differential
    - Metabolic panel (fasting)
    - Hepatic function panel
    - Lipid panel (fasting)
    - Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential
- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred to an independent laboratory before end of the enrolment period.

The investigator should plan the MRI so that the results are available prior to the V2/M0 visit to insure image quality.

The patient will be provided with ambulatory activity monitoring device (Fitbit ®) and instructions for use.

The patient will be assigned with an inclusion number automatically provided by the IWRS system. This unique inclusion number will not be re-allocated in case of screen failure.

2.6.3.1.2 Visit 2 (M0): Randomization visit

If the patient fulfils all inclusion/exclusion criteria at this visit, the patient will be randomized. Then, the investigator/study coordinator will record the following information into the eCRF:

- Any adverse event occurred before the randomization visit
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- SDMT
- MSQOL-54 / CAREQOL-MS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test (If applicable)
- Brain MRI
- ECG 12 derivations (triplicate)
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will fill a "drug delivery form" for the hospital pharmacy (where applicable) to dispense study medication.

The patient will be supplied with the study medication dispensed by the hospital pharmacy or the principal investigator where applicable. Four vials for a total of three months of treatment will be dispensed. The patient will be asked to take one capsule from the vial in the morning, one capsule at noon and one capsule in the evening. Capsules have to be swallowed with a glass of water with a minimum of 4 hours between each intake and at least one hour before mealtime.

2.6.3.1.3 Visit 3 (M3): Follow up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection

- Urinary-based pregnancy test results of the period V2/M0 to V3/M3
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator should ideally plan to carry out the brain MRI of the V4/M6 visit on the same day. However, if this is not possible, the MRI should be performed as per the permitted window within the protocol (+/-10 days).

2.6.3.1.4 Visit 4 (M6): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Brain MRI
- Urinary-based pregnancy test results of the period V3/M3 to V4/M6
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will perform blood sampling and shipment to the Central Clinical Laboratory of the safety panel following the Operating Manual:

- Safety panel includes:
  - CBC with differential
  - Metabolic panel
  - Hepatic function panel
  - Lipid panel (fasting)
  - Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential
  - Thyroid panel: TSH, T3 free
- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred at the end of the study to an independent laboratory. The date and time of the last biotin intake will be collected in the eCRF.

2.6.3.1.5 Visit 5 (M9): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V4/M6-V5/M9 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

2.6.3.1.6 Visit 6 (M12): Follow up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V5/M9-V6/M12 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it
- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred at the end of the study to an independent laboratory. The date and time of the last biotin intake will be collected.

The investigator will plan the brain MRI of the V7/M15 visit ideally on the same day. However, if it is not possible, the MRI should be performed as per the permitted window within the protocol (+/- 15 days).

2.6.3.1.7 Visit 7 (M15): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- SDMT
- CGI-I (SGI, CGI)
- MSQOL-54 / CAREQOL-MS
- Ambulatory activity monitoring data collection
- Physician and patient treatment assignment questionnaire
- Brain MRI
- ECG 12 derivations (single)
- Urinary-based pregnancy test results of the V6/M12-V7/M15 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will perform blood sampling and shipment to the Central Clinical Laboratory of the safety panel following the Operating Manual:

- Safety panel includes:
    - CBC with differential
    - Metabolic panel
    - Hepatic function panel

- Lipid panel (fasting)
- Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential
- Thyroid panel: TSH, T3 free

- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred at the end of the study to an independent laboratory. The date and time of the last biotin intake will be collected.

Patients who have completed 15 months will be kept on the blinded study drug until the last Month 15 evaluation for all study subjects has been completed but not more than 27 months.

Once the last month 15 evaluation of the study has been completed, patients will switch to the active drug at the next planned study visit (V8/M18 or V9/M21 or V10/M24 depending on their randomization date). Participants and study personnel will remain blinded as to the original treatment assignment.

Dispensation of the active drug to all patients will be triggered automatically by IWRS at the last V7/M15 evaluation of the study and for all subsequent visits.

2.6.3.1.8 Visit 8 (M18): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V7/M15-V8/M18 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The patient will be provided with the study drug dispensed by the hospital pharmacy or the Principal Investigator where applicable and will be treated with the active drug once the last V7/M15 evaluation of the study has been completed. Alternatively, the patient will remain on double-blind.

2.6.3.1.9 Visit 9 (M21): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS

- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V8/M18-V9/M21 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The patient will be provided with the study drug dispensed by the hospital pharmacy or the Principal Investigator where applicable and will be treated with the active drug once the last V7/M15 evaluation of the study has been completed. Alternatively, the patient will remain on double-blind.

2.6.3.1.10 Visit 10 (M24): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V9/M21-V10/M24 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The patient will be provided with the study drug dispensed by the hospital pharmacy or the Principal Investigator where applicable and will be treated with the active drug once the last V7/M15 evaluation of the study has been completed. Alternatively, the patient will remain on double-blind.

The investigator should ideally plan the brain MRI of the V11/M27 visit on the same day. However, if it is not possible, the MRI should be performed as per the permitted window within the protocol (+/- 15 days)

2.6.3.1.11 Visit 11 (M27): Final double-blind visit of part 1

The investigator will record the following information into the eCRF:

- Informed consent for part 2 (Open Label Extension)
- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- SDMT
- CGI-I (SGI, CGI)
- MSQOL54 / CAREQOL-MS
- Ambulatory activity monitoring data collection
- Brain MRI
- ECG 12 derivations (single)
- Urinary-based pregnancy test results of the V10/M24-V11/M27 period

- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will perform blood sampling and shipment to the Central Clinical Laboratory of the safety panel following the Operating Manual:

- Safety panel includes:
  - CBC with differential
  - Metabolic panel
  - Hepatic function panel
  - Lipid panel (fasting)
  - Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential
  - Thyroid panel: TSH, T3 free
- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred at the end of the study to an independent laboratory. The date and time of the last biotin intake will be collected.

At this visit, participants will be offered entry into an open label extension (OLE) where all patients will be treated with active drug (MD1003) until the end of the study (V18/M66). Four vials for a total of 3 months of treatment will be dispensed to the patient.

Dispensation of the active drug at the V11/M27 visit and for subsequent OLE (Part 2) visits will be automatically programmed by IWRS.

Patients and study personnel will remain blinded to the original treatment arm until the last V11/M27 visit of the study has been completed.

The randomization list of each site will be communicated once the last V11/M27 visit of the study for all subjects has been completed.

If a patient decides not to participate in the OLE, he should be followed-up for 30 days after receiving the last dose of study medication and any AEs, which occur during this time, should be reported in the eCRF and followed up until resolution or stabilization of the AE or SAE.

The investigator will remind women of child bearing potential not willing to enter the OLE to perform a monthly urinary pregnancy test for a period up to 3 months following the treatment discontinuation and inform the site immediately in case of positive result in order to organize an additional visit.

2.6.3.2 Evaluations Part 2: Open-label extension phase

2.6.3.2.1 Visit 12 (M30): Follow up visit of part 2 (OLE)

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V11/M27-V12/M30 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

Seven vials for a total of six months of treatment will be dispensed to the patient.

2.6.3.2.2 Visit 13 (M36): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V12/M30-V13/M36 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will plan the brain MRI of the V14/M42 visit ideally on the same day. However, if it is not possible, the MRI should be performed as per the permitted window within the protocol (+/- 15 days).

2.6.3.2.3 Visit 14 (M42): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- CGI-I (SGI, CGI)
- MSQOL-54 / CAREQOL-MS
- Ambulatory activity monitoring data collection
- Brain MRI
- ECG 12 derivations (single)
- Urinary-based pregnancy test results of the V13/M36-V14/M42 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will perform blood sampling and shipment to the Central Clinical Laboratory of the safety panel following the Operating Manual:

- Safety panel includes:
    - CBC with differential
    - Metabolic panel
    - Hepatic function panel
    - Lipid panel (fasting)
    - Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential
    - Thyroid panel: TSH, T3 free

- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred at the end of the study to an independent laboratory. The date and time of the last biotin intake will be collected.

2.6.3.2.4 Visit 15 (M48): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V14/M42-V15/M48 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will plan the brain MRI of the V16/M54 visit ideally on the same day. However, if it is not possible, the MRI should be performed as per the permitted window within the protocol (+/- 15 days).

2.6.3.2.5 Visit 16 (M54): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- CGI-I (SGI, CGI)
- MSQOL-54 / CAREQOL-MS
- Ambulatory activity monitoring data collection
- Brain MRI
- ECG 12 derivations (single)
- Urinary-based pregnancy test results of the V15/M48-V16/M54 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will perform blood sampling and shipment to the Central Clinical Laboratory of the safety panel following the Operating Manual:

- Safety panel includes:
    - CBC with differential
    - Metabolic panel
    - Hepatic function panel
    - Lipid panel (fasting)
    - Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential

- Thyroid panel: TSH, T3 free

- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred at the end of the study to an independent laboratory. The date and time of the last biotin intake will be collected.

2.6.3.2.6 Visit 17 (M60): Follow-up visit

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Urinary-based pregnancy test results of the V16/M54-V17/M60 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will plan the brain MRI of the V17/M60 visit ideally on the same day. However, if it is not possible, the MRI should be performed as per the permitted window within the protocol (+/- 15 days).

2.6.3.2.7 Visit 18 (M66): Final visit of OLE

The investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Compliance evaluation since the previous visit
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- CGI-I (SGI, CGI)
- MSQOL-54 / CAREQOL-MS
- Ambulatory activity monitoring data collection
- Brain MRI
- ECG 12 derivations (single)
- Urinary-based pregnancy test results of the V17/M60-V18/M66 period
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will perform blood sampling and shipment to the Central Clinical Laboratory of the safety panel following the Operating Manual:

- Safety panel includes:
  - CBC with differential
  - Metabolic panel
  - Hepatic function panel
  - Lipid panel (fasting)

  - Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential
  - Thyroid panel: TSH, T3 free
- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred at the end of the study to an independent laboratory. The date and time of the last biotin intake will be collected.

The investigator will remind women of child bearing potential to perform a monthly urinary pregnancy test for a period up to 3 months following the treatment discontinuation and inform the site immediately in case of positive result in order to organize an additional visit. During this visit the investigator will complete a pregnancy follow-up form and initiate the follow-up of the patient up to the delivery whatever its outcome.

Participants should be followed-up for 30 days after receiving the last dose of study medication and any AEs, which occur during this time, should be reported in the eCRF and followed up until resolution or stabilization of the AE or SAE.

2.6.3.3 Unscheduled Visit (when required)

In case of relapses or whenever required by the patient or investigator, the patient can attend an unscheduled visit where the investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)
- Concomitant medication and therapies
- Clinical examination including vital signs
- EDSS
- TW25
- C-SSRS
- Ambulatory activity monitoring data collection
- Brain MRI in case of relapse
- ECG 12 derivations
- SPI2 patient alert card dispensed to patient with next visit date indicated on it

The investigator will perform blood sampling and shipment to the Central Clinical Laboratory of the safety panel following the Operating Manual:

- Safety panel includes:
  - CBC with differential
  - Metabolic panel
  - Hepatic function panel
  - Lipid panel (fasting)
  - Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential
  - Thyroid panel: TSH, T3 free

2.6.3.4 Early Termination Visit (when applicable)

In case of early termination, the patient should attend an early termination visit where the investigator will record the following information into the eCRF:

- Adverse events
- MS relapse assessment questionnaire (specific form, Cf. Annex 3)

- Concomitant medication and therapies
- EDSS
- TW25
- C-SSRS
- SDMT
- CGI-I (SGI, CGI)
- MSQOL-54 / CAREQOL-MS
- Ambulatory activity monitoring data collection
- Physician and patient treatment assignment questionnaire (not applicable for open-label extension)
- ECG 12 derivations (single)

The investigator will perform blood sampling and shipment to the Central Clinical Laboratory of the safety panel following the Operating Manual:

- Safety panel includes:
    - CBC with differential
    - Metabolic panel
    - Hepatic function panel
    - Lipid panel (fasting)
    - Blood-based pregnancy test: highly sensitive HCG pregnancy test in women of childbearing potential
    - Thyroid panel: TSH, T3 free
- A serum sample for biotin and neurofilament level assessment will be stored at -20° on site and transferred at the end of the study to an independent laboratory. The date and time of the last biotin intake will be collected.

The investigator will remind women of child bearing potential to perform a monthly urinary pregnancy test for a period up to 3 months following the treatment discontinuation and inform the site immediately in case of positive result in order to organize an additional visit.

Participants should be followed-up for 30 days after receiving the last dose of study medication and any AEs, which occur during this time, should be reported in the eCRF and followed up until resolution or stabilization of the AE or SAE.

2.7 **Efficacy assessments**

For efficacy assessment, all scales and questionnaires will be provided and have to be used for this study unless site specific versions are approved by the sponsor.

2.7.1 Expanded Disability Status Scale (EDSS) Definition

Neurostatus EDSS (Cf. Annex 2) will be used during the study to rate neurological impairment in multiple sclerosis patients. The Neurostatus is a modification by Kappos of the original Kurtzke scale. It eliminates some ambiguities especially for the ambulation score.

Kurtzke's Expanded Disability Status Scale (EDSS) is a scale for assessing neurologic impairment in MS (Kurtzke, 1983) including: 1) a series of scores in each of eight functional systems, and 2) the EDSS steps (ranging from 0 [normal] to 10 [death due to MS]). The functional systems are visual, brain stem, pyramidal, cerebellar, sensory, bowel & bladder, cerebral, and other functions.

EDSS steps 4.5 to 7.5 are defined by the impairment to ambulation and rely on a specific ambulatory score:

Expanded disability status scale:

0: Normal neurological exam (all FS grade 0)
1.0: No disability, minimal signs in one FS (one FS grade 1)
1.5: No disability, minimal signs in more than one FS (more than one FS grade 1)
2.0: Minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5: Minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0: Moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three / four FS grade 2, others 0 or 1) though fully ambulatory
3.5: Fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one / two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1); or fully ambulatory with five FS grade 2 (others 0 or 1)
4.0: Ambulatory without aid or rest for > 500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
4.5: Ambulatory without aid or rest for > 300 meters; up and about much of the day, characterized by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0: Ambulatory without aid or rest for > 200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5: Ambulatory without aid or rest for >100 meters
6.0: Unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting (see chapter 8, Ambulation)
6.5: Constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting (see chapter 8, Ambulation)
7.0: Unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5: Unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0: Essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5: Essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0: Helpless bed patient; can communicate and eat
9.5: Totally helpless bed patient; unable to communicate effectively or eat/swallow
10: Death due to MS

Ambulation score rated from 0 to 12:

0: Unrestricted
1: Fully ambulatory
2: ≥300 meters, but <500 meters, without help or assistance (EDSS 4.5 or 5.0)
3: ≥200 meters, but <300 meters, without help or assistance (EDSS 5.0)
4: ≥100 meters, but <200 meters, without help or assistance (EDSS 5.5)
5: Walking range <100 meters without assistance (EDSS 6.0)
6: Unilateral assistance, ≥50 meters (EDSS 6.0)
7: Bilateral assistance, ≥120 meters (EDSS 6.0)
8: Unilateral assistance, <50 meters (EDSS 6.5)
9: Bilateral assistance, ≥5 meters, but <120 meters (EDSS 6.5)

10: Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)

11: Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)

12: essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0)

2.7.1.1 EDSS requirements and measurement method

EDSS including ambulatory part must be completed at each visit and recorded using Neurostatus scoring sheet.

The reported walking distance must be a measured value and not declarative or a rounded value. The ambulation should be done in an inside hallway of sufficient length (At least 30m) with a reliable consistent method of measurement. The site should ensure that patients are assessed at approximately the same time of day whenever possible (Morning vs afternoon visit can impact EDSS assessment).

The following measuring methods are allowed:

- Measuring wheel
- Marks in the corridor associated with any other complementary methods (measuring tape or wheel to measure the distance between 2 marks…) allowing to report the most accurate distance
- Any other measuring method that allow to report an accurate and reliable walking distance.

The measuring method used should be documented in source documents.

Patient reported distance values cannot replace the measurements performed at each study visit on site.

If a patient is fully ambulatory or unrestricted, the blinded rater should ensure that the patient walks more than the 500 meters threshold in order to avoid any ambiguity in the EDSS score.

2.7.1.2 EDSS assistive device

As the frame of reference for the primary endpoint is improvement, there are instances in which patients may need to be tested, safely, without assistance. For example, patients using a cane or walker to ambulate should be examined safely with less assistance (e.g. from bilateral assistance to unilateral assistance) or no assistance (from unilateral assistance to no assistance).

Remember that all patients must be evaluated the same way all along the study from the screening date.

The blinded rater will perform the neurological examination, document the Kurtzke Functional Systems (KFS) scores and ambulation score, then assess EDSS.

Every effort will be made to ensure that there is no change in the blinded rater throughout the course of the study for any individual patient or at least the same rater for V1/M-1, V2/M0, V6/M12, and V7/M15.

Blinded raters will receive training in performing EDSS assessments prior to the beginning of the study and must have successfully passed an examination on performance of the Neurostatus EDSS examination within 24 months of participation. A blinded rater is not necessarily a physician but can be a study nurse as long as trained to perform the EDSS and Neurostatus level C certified. In case of a change of blinded rater during the study, the new blinded rater should acknowledge and approve the previous EDSS score for all concerned patients.

2.7.1.3 Definition of EDSS improvement and worsening

For the EDSS, the baseline value will be the best of the 2 scores obtained at either the inclusion or randomization visits.

According to baseline EDSS, an improvement will be defined as follows:

- EDSS from 3.5 to 5.5: decrease of at least 1 point
- EDSS at or above 6: decrease of at least 0.5 point

According to baseline EDSS, a worsening will be defined as follows:

- EDSS from 3.5 to 5.5: increase of at least 1 point
- EDSS at or above 6: increase of at least 0.5 point

2.7.2 TW25 (Timed 25-Foot Walk)

The TW25 is a widely used outcome measure of leg function/ambulation. It has been validated in progressive MS trials (Goodman et al., 2009).

In this test the patient should walk 7.62 meters (25 feet) as quickly, but safely, as possible without running. The course on which the test is walked, such as a hallway, should be clearly marked and free of obstructions. Patients are permitted to use their own assistive device or the best assistive device that might be necessary.

If a device is necessary (EDSS above 6), at the inclusion visit, the device should be used as well during all the subsequent follow-up visits even if the patient improved.

The timed-walk test should be performed twice, the time being recorded in seconds to the nearest one-tenth of a second, starting as the lead foot passes the start line and ending as the lead foot passes the finish line.

The two values of TW25 will be entered in the eCRF. Please document any condition that could affect the realization of the test.

The TW25 will be performed at each visit by the blinded rater. A blinded rater is not necessarily a physician but can be a study nurse as long as trained to perform the TW25 test.

2.7.2.1 Definition of TW25 improvement and worsening

For the TW25, the baseline value will be the best mean of the 2 scores obtained at either the inclusion or randomization visits (the lowest mean between the 2 visits). An improvement is defined as a TW25 decreased by at least 20% and a worsening is defined as an increase of 20%.

The TW25 value at visit M12 is defined as the mean of the two TW25 attempts at visit M12. The TW25 value at visit M15 is defined as the mean of the two TW25 attempts at visit M15.

2.7.3 Symbol Digit Modalities Test (SDMT)

The SDMT measures the time to pair abstract symbols with specific numbers. The test requires elements of attention, visual perceptual processing, working memory, and cognitive/psychomotor speed. The SDMT is a measure of divided attention, visual scanning and motor speed. This measure involves a coding key consisting of 9 abstract symbols, each paired with a number ranging from 1 to 9. The subject

is required to scan the key and write down the number corresponding to each symbol as fast as possible. The number of correct substitutions within 90 seconds is recorded. In the written version of the test the subject fills in the numbers that correspond to the symbols. In the oral version the examiner records the numbers spoken by the subject. The score is the number of correctly coded items from 0-110 in 90 seconds.

The written form from Western Psychological Services (WPS) will be used in the trial. The oral version can be used in the study if the patient has upper extremity impairment. If a patient switches from written to oral version during the study, it should be documented accordingly.

2.7.4 Remote monitoring of ambulatory activity

Remote monitoring of ambulatory activity will be performed using a Fitbit device. The key variable will be the average daily step count over 1-week period recorded continuously in the natural environment as part of routine daily activity. This is the measure most frequently used in physical activity trials as it has good face validity and has ample validation against research grade accelerometers. Other variables that can also be measured using this kind of device include: estimated active minutes per day; estimated distance walked; estimated stairs climbed (# of floors); estimated energy expenditure (calories burned); sleep (awake vs. restless vs. asleep).

Participants will be trained by the investigational team on the set-up, use and maintenance of the device and asked to wear the device as much as possible for the duration of the study. These devices have the ability to be motivational by setting daily step count goals. To minimize the influence of motivational factors on ambulatory activity levels, the daily “goal” on the device will be set low (i.e. 500 steps/day) or at least standardized, although participants can be taught how to change the settings to their liking (these settings do not affect the number of steps stored by the device).

The site should encourage the patients to keep wearing the Fitbit device during Part 2 of the study.

2.7.5 Patient reported outcome measures

Patient reported outcome measures will be collected to compare the patient outcomes in active and placebo groups.

The following instruments will be administered:

- Subject Global Impression of Improvement scale (SGI)
- Multiple Sclerosis Quality of Life-54 (MSQOL-54)
- Caregiver health-related quality of life in Multiple Sclerosis (CAREQOL-MS)

2.7.5.1 Clinical Global Impression of Improvement scale (CGI-I)

The Clinical Global Impression of Improvement scale (CGI-I) is a 7-point scale that requires the clinician and the patient to assess how much the patient's illness has improved or worsened relative to the baseline state at the beginning of the intervention and rated as: 1, very much improved; 2, much improved; 3, minimally improved; 4, no change; 5, minimally worse; 6, much worse; or 7, very much worse.

The CGI-I will be assessed by the patient (subject global impression, SGI) and by the clinician (clinician global impression, CGI) at V7/M15, V11/M27, V14/M42, V16/M54, and V18/M66.

2.7.5.2 Multiple Sclerosis Quality of Life-54 (MSQOL-54)

The MSQOL-54 is a multidimensional health-related quality of life measure that combines both generic and MS-specific items into a single instrument (Vickrey *et al.*, 1997, Vickrey *et al.*, 1995). The developers utilized the SF-36 as the generic component to which 18 items were added to tap MS-specific issues such as fatigue, cognitive function, etc. This 54-item instrument generates 12 subscales along with two summary scores, and two additional single-item measures. The subscales are: physical function, role limitations-physical, role limitations-emotional, pain, emotional well-being, energy, health perceptions, social function, cognitive function, health distress, overall quality of life, and sexual function. The summary scores are the physical health composite summary and the mental health composite summary. The single item measures are satisfaction with sexual function and change in health.

2.7.5.3 Caregiver health-related quality of life in Multiple Sclerosis (CAREQOL-MS)

In 2011, Benito-León et al. published the first specific questionnaire for assessing the QoL of carers of patients with MS: Caregiver Health-Related Quality of Life in Multiple Sclerosis (CAREQOL-MS). It consists of 24 items comprising four subscales: physical stress/global health, social integration, emotion, and the need for assistance/emotional reactions. Questionnaire items were derived from a literature review and the views of patients, caregivers, and experts. They are scored on a 5-point Likert-type scale (higher scores reflecting worse HRQoL). A significant correlation was observed between the CAREQOL-MS score and carers' age and patients' EDSS scores. The average standard error for the subscales ranged from 2.01 to 2.43. The scale was free of floor or ceiling effects. For subscales, Cronbach's alpha coefficient ranged from 0.80 to 0.90. These results gave evidence for the usefulness and satisfactory psychometric properties of the questionnaire CAREQOL-MS (see Appendix 4). Therefore, CAREQOL-MS will be completed if patient has a caregiver. In the event the subject's caregiver changes during the course of the study, this would be considered as a protocol deviation and should be reported appropriately.

2.8 **Safety assessments**

Serious AE will be reported immediately to the Pharmacovigilance Unit of the sponsor within 24h after awareness from investigational team.

2.8.1 Serious and non-serious adverse events monitoring and recording

All adverse events will be recorded throughout the study from signature of the informed consent form.

2.8.2 Suicide behavior questionnaire: Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (both Baseline and Since Last Visit paper versions) will be administered to the patient and scored by a qualified, trained rater. Additional detailed information concerning administration, scoring and recording may also be provided by the Rater Training Vendor. Training is recommended for clinical practice before completing the C-SSRS.

2.8.2.1 Inclusion

Suicidal ideation and behaviour will be assessed at inclusion visit using the Baseline C-SSRS. The Baseline C-SSRS should be administered by trained raters. Subjects with a history of suicidal ideation as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the C-SSRS

completed at the inclusion visit or history of a suicide attempt regardless of the attempt date (per the C-SSRS) will not be included.
There is no predefined C-SSRS score to exclude a patient from participating in the trial. However, only patients who are not judged to be at serious risk for self-harm during the course of the trial may be included in the trial; others must be excluded from trial participation and receive appropriate clinical care to ensure their safety.

2.8.2.2 Follow up visits

Suicidal ideation and behaviour will be assessed during this trial using the Since Last Visit C-SSRS. The Since Last Visit C-SSRS should be administered by trained raters at each visit, as indicated in the flow chart, as well as at unscheduled visits as clinically indicated. Site staff should review the contents of the C-SSRS for completeness and then transcribe the data to the eCRF. Patients who at any time during this trial report an AE of suicidal ideation or behaviour, either between visits or during visit interviews, must be assessed by trained raters and reviewed by an M.D. or a clinician Ph.D. Patients who report suicidal ideation with intent, with or without a plan or method (i.e., a positive response to Items 4 or 5 in the assessment of suicidal ideation on the C-SSRS) or suicidal behaviour must be evaluated that day by a psychiatrist or other trained mental health professional who is a licensed psychologist, social worker or nurse practitioner (or comparable professional qualification in countries outside the United States). Only patients whose suicidal ideation is passive, who expressly deny any intent to act, and who, after evaluation, are not judged to be at serious risk for self-harm during the course of the trial may continue in the trial; others must be discontinued from trial participation and receive appropriate clinical follow-up care to ensure their safety. All reports of suicidal ideation or behaviour must be reported as an AE and as an event of special interest Sites are to indicate which health care professionals are to be responsible for acute care on-site and to specify referral center(s) to be used for further evaluation. The C-SSRS (both Baseline and Since Last Visit paper versions) will be administered to the patient and scored by a qualified, trained rater. Additional detailed information concerning administration, scoring and recording may also be provided by the Rater Training Vendor.

Training is recommended for clinical practice before completing the C-SSRS.

2.8.3 Clinical examination

2.8.3.1 Physical examination

The physical examination comprises a routine medical examination including neurological and cognitive assessments. The following body systems will be examined: HEENT (head, eyes, ear, nose, and throat), urological, cardiovascular, respiratory, lymphatic, gastrointestinal, musculoskeletal, dermatological, and venous system.

2.8.3.2 Vital signs

The following vital signs will be assessed at each visit (except when mentioned):

- Systolic (SBP) and diastolic (DBP) blood pressure (mmHg);
- Heart rate (beats per minute [bmp]);
- Body temperature (°C);
- Height* (cm) and weight (kg).

*Height will be assessed and recorded only at V1/M-1.

Blood pressure (SBP and DBP) and heart rate will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size. Supine blood pressure and heart rate will be measured after the patient has rested in a supine position for at least 5 minutes.
Body temperature will be measured until a stable reading is obtained.

2.8.4 Laboratory testing (haematology and biochemistry panel)

Laboratory testing (standard haematology and biochemistry panel) including:

- CBC with differential:
  - Number and types of white blood cells (WBCs)
  - Number of red blood cells (RBCs)
  - Red cell distribution width (RDW)
  - Haematocrit
  - Haemoglobin
  - Mean corpuscular volume (MCV)
  - Mean corpuscular haemoglobin
  - Platelet count
- Metabolic panel (fasting):
  - BUN
  - CO2 (carbon dioxide/bicarbonate)
  - Creatinine
  - Estimated creatinine clearance rate using Cockcroft-Gault formula
  - Glucose
  - Serum chloride
  - Serum potassium
  - Serum sodium
- Hepatic function panel:
  - Aspartate transaminase (AST)
  - Alanine transaminase (ALT)
  - Bilirubin
  - Gamma-glutamyl transpeptidase (GGT)
  - Alkaline phosphatase
- Lipid panel (fasting):
  - Total cholesterol
  - Triglycerides
  - HDL cholesterol
  - LDL cholesterol
- Contraceptive method monitoring in women of childbearing potential
  - Highly sensitive HCG pregnancy test
- Monthly urinary pregnancy tests
- Thyroid panel:
  - Thyroid-Stimulating Hormone (TSH)
  - Free Triiodothyronine (T3 free)

2.8.5 Electrocardiogram

Digital ECG will be recorded during Part 1 at V2/M0 (triplicated ECG), V7/M15, V11/M27, during Part 2 at V14/M42, V16/M54, and V18/M66 to assess the potential of MD1003 to delay cardiac repolarization. All ECG records should be electronically sent to the Core Cardiac Safety Laboratory (CCSL). In case the electronic submission of the ECG is not possible, the original paper ECG trace should be sent to the CCSL.

The assessment will be performed by the CCSL and include testing the effects on the QT/QTc interval as well as the other ECG parameters (RR, PR, QRS intervals, wave morphology, rhythm and conduction).

QTc interval will be calculated using Fridericia's correction: $QTc = QT/RR^{0.33}$

The QT/QTc interval data will be assessed both as analyses of central tendency (e.g., means, medians) and categorical analyses.

For central tendency, the effect of MD1003 on the QT/QTc interval will be analysed using the largest time-matched mean difference between the drug and placebo (baseline-adjusted) over the collection period.

For categorical analysis, QT/QTc interval data will be based on the number and percentage of patients meeting or exceeding some predefined upper limit values:

- Absolute QTc interval prolongation
  - QTc interval > 450
  - QTc interval > 480
  - QTc interval > 500
- Change from baseline in QTc interval:
  - QTc interval increases from baseline >30
  - QTc interval increases from baseline >60
- Statements regarding other ECG anomalies (rhythm, conduction, repolarisation) and their change from baseline will be reported and analysed

2.8.6 Brain MRI

Brain MRI using conventional sequences (T2 and T1 pre and post gadolinium injection) will be performed during Part 1 at V2/M0, V7/M15, V11/M27, during Part 2 at V14/M42, V16/M54, and V18/M66. Safety of MD1003 will be assessed by analysing:

- Comparison of proportion of patients with at least one new/enlarging T2-weighted MS lesion at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
- Mean number of new/enlarging T2-weighted MS lesions per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
- Comparison of proportion of patients with at least one gadolinium enhancing lesion on the T1-weighted sequence at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
- Mean number of gadolinium enhancing lesions on the T1-weighted sequence at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
- Mean of T2-weighted lesion volume per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)
- Mean of non-enhancing T1-weighted lesion volume per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo)

2.9 **Exploratory endpoints assessed by brain MRI**

The brain MRI will be supervised and analysed centrally by a Core Imaging Laboratory. Technical specifications will be described in a separate MRI Manual containing scanner-specific console instructions for acquisition, as well as data transfer requirements.

As a pre-requisite, all sites will be trained to perform and transfer to Core Imaging Laboratory a dummy run before first patient enrolled. Site will be authorized to start enrolment upon Approval Letter from Core Imaging Laboratory receipt.

During the study, DICOM images will be transferred to the Core Imaging Laboratory. After Quality Control, analyses will be performed blindly.

The brain MRI also will assess the following endpoints between V2/M0 and V7/M15, between V2/M0 and V11/M27, and between V2/M0 and each MRI time point during the open label extension:

- Percent thalamic volume change
- Percent whole brain volume change
- Percent cortical grey matter volume change
- Brain water content by Pseudo T2 relaxation time change
- NAA/Cr in a subset of sites acquiring MRS

2.10 Measures of biotin concentration in blood

Since biotin is available as a food supplement in several countries, the absence (or low level) of biotin intake will be checked at inclusion by measuring biotin plasma concentration.

Other measures will be performed at V4/M6, V6/M12, V7/M15, V11/M27 or at early termination during the placebo-controlled phase to check compliance in patients treated by MD1003 and to check for absence of "off label" biotin intake in patients having received the placebo. Additionally, biotin measures will be performed in Part 2 at V14/M42, V16/M54, and V18/M66 or at early termination to assess compliance.

The biotin assay will be performed blindly in an independent central laboratory which has no contact with the investigators. A plasma level above 75 ng/ml will be considered as an important exposure. This threshold corresponds to the lowest concentration value observed during the previous clinical trials with high doses biotin at steady state.

Pre-treatment samples will be dosed before the end of the enrolment period (i.e. after 3 months of enrolment) to check the proportion of "off label" use of high dose biotin in the placebo group. The double-blind will be maintained by the central laboratory and individual results will be disclosed to Steering Committee only in case of protocol violation, allowing to envision the patient's withdrawal and replacement before the end of the enrolment period.

Biotin and its main metabolites (BNB and BSO) measures of V4/M6, V6/M12 and V7/M15 samples will be performed at the end of the study with no access to data prior to database lock. The placebo patients found as biotin positive (above the 75 ng/ml threshold) will be considered as a protocol violation and withdrawn from the FAS and PP analysis.

The treating and evaluating physicians will not have access to the results before the end of the study at V11/M27.

2.11 Measures of neurofilament concentration in blood

The purpose of the neurofilament assay is to serve as an independent assessment of neuroinflammation.

Neurofilament concentrations will be measured in Part 1 at V1/M-1, V4/M6, V6/M12, V7/M15, V11/M27 and in Part 2 at V14/M42, V16/M54, and V18/M66.

The neurofilament concentration will be performed blindly in an independent central laboratory which has no contact with the investigators.

The treating and evaluating physicians will not have access to the results before the end of the study at V11/M27.

3 ADVERSE EVENTS

3.1 Special warning, precaution for use related to interference with laboratory tests

Biotin may interfere with some immunoassay methods that use a biotinylated reagent i.e. based on a biotin/streptavidin interaction. Therefore special consideration must be given to patients requiring biological tests outside the Central Laboratory used in the study. The impacted laboratory tests include those for anaemia, cardiac, fertility, pregnancy, hormonal, oncology, bone metabolism, inflammation biomarkers, infectious disease antigens and antibody titration. Some immunohistochemistry methods used in diagnostic pathology may also be affected. The following needs to be taken into account:

- Only biotin/streptavidin-free analyzers and kits are suitable for performing immunoassays.
- To avoid misleading results, clinical laboratories should be informed that the patient is taking high dose biotin so that appropriate analyzers can be used to ensure accuracy and reliability.
- When interpreting laboratory test results performed outside the study in a patient treated with MD1003, it is necessary to contact the laboratory to verify if the treatment with high biotin doses interferes with the method used. If this is the case, the test should be repeated using an alternative method.
- Tests that are sometimes required in an emergency situation can be distorted by biotin. They include, but are not limited to, βHCG, BNP, CPK, CPKMB, D-dimer, troponin, cortisol, procalcitonin TSH, T3/T4, HIV serology.
- The results can be falsely high, but also falsely low, dependant on the type of assay used:
  - Competitive assays are used for low molecular weight molecules (such as T3, T4, cortisol, testosterone, 25OH vitamin D, ...) with a risk of falsely high results
  - Sandwich assays are used for high molecular weight molecules (such as TSH, troponin, ACTH, βHCG, PSA ...) with a risk of falsely low results
- Patients and their caregiver should be informed about the risk of interference with some diagnostic and laboratory tests and are strongly advised to carry with them at all times the SPI2 patient alert card summarizing this information. The patient alert card should be given to patients at inclusion. At each visit, the investigator should verify that the patient understands this important warning and redistribute a new copy of the alert card to the patient. This card should be presented to all healthcare professionals that the patient sees, including in an emergency situation.
- General Practitioner (GP) letter: If a patient has consented to it, a letter must be sent to patient's GP to inform them that their patient is potentially taking high dose biotin and of the potential risk of laboratory interferences due to biotin. During the study the blinded rater will and must remain blinded from all biological tests dosed outside the Clinical Central Laboratory.

In case of a laboratory test performed outside of SPI2 routine safety assessments, the site must verify whether the laboratory results were affected by biotin interferences. The site should immediately check the model of the analyser used and perform a re-test in a laboratory using suitable analysers. The CSM can provide sites with the closest location of a laboratory equipped with a suitable analyser upon request.

If any treatment has been initiated following laboratory results outside of the study, the site should immediately ask the patient to stop the corrective treatment in case this diagnosis was based on non-reliable laboratory results.

If it is confirmed that the laboratory results were impacted by interferences, the initial verbatim of the AE reported in the eCRF should be replaced by "False [initial AE verbatim] due to interferences with biotin."

3.2 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment.

An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of an investigational product, whether or not considered related to the IP.

Examples of AEs include, but are not limited to, the following:

- Abnormal test findings (i.e. laboratory interferences)
- Hypersensitivity
- Progression/worsening of underlying disease
- Drug abuse
- Drug dependency
- Protocol-related adverse event (see definition below)
- Additionally, they may include the signs or symptoms resulting from
- Drug overdose
- Drug withdrawal
- Drug misuse
- Drug interactions
- Exposure during pregnancy
- Exposure via breastfeeding
- Medication error

A protocol-related adverse event is an AE occurring during a clinical study that is not related to the IP but is considered to be related to the research conditions, i.e., related to the fact that a patient is participating in the study. For example, a protocol-related AE may be an untoward event related to a medical procedure required by the protocol like for example, ocular injuries due to the instillation procedure.

Serious Adverse Event (SAE):

A serious adverse event (SAE) is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening, (Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if more severe.)
- Requires hospitalization or prolongation of existing hospitalization
- Results in disability/incapacity
- Is a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of other outcomes listed in the above definition. These should also be considered serious.
- In this study, all MS relapses (as defined below) will be considered as a SAE. Study treatment should be maintained as much as possible.
    - All MS relapses (as defined below) reported by investigators will be recorded in an MS relapse form (annex 3) which will be communicated to and assessed by the Adjudication Committee for diagnosis validation.

MS relapses

The following definitions should be used for relapses:

- Protocol-defined relapse:
  - appearance of a new symptom or worsening of an old symptom, attributable to MS
  - symptoms lasting at least 24 hours
  - absence of fever or infection
  - preceded by stability or improvement for at least 30 days
  - subject seen within 7 days of onset
  - change of at least 0.5 on EDSS or 1 pt on 2 FS or 2 pts on 1 FS since the last visit
- Non protocol-defined relapse: same as above but the subject was not seen within 7 days of onset
- Suspected relapse: Relapse that fails to meet the above situations but may have been a relapse – i.e. all circumstances point to relapse, but no change in the EDSS.

It is asked to the sites to interview patients at each visit using the relapse assessment questionnaire in order to record all reports of possible relapses. This form will be submitted and reviewed by the Clinical Adjudication Committee in case of protocol-defined, non-protocol-defined and suspect relapses. The event fulfilling the "Not a relapse" criteria should NOT be submitted to the Clinical Adjudication Committee.

Medication Errors

In this protocol, a reportable medication error includes the following:

- The administration of an unassigned treatment.
- Inadvertent or accidental exposure to an investigational product with or without an AE.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated adverse event(s) is captured on an adverse event (AE) eCRF (refer to Adverse Event Reporting section for further details).

Important:

- All AE/SAE associated or not to the IPs shall be notified to the Sponsor Pharmacovigilance Unit.
- SAR suspected to be related to an interaction between an IP and a Non-Investigational Product (NIP) should be reported.

3.3 Handling of Non-Serious Adverse Events

All AEs encountered during the clinical study (from signature of informed consent) will be reported on the eCRF.

- All AEs and SAEs must be recorded on patient's source documents.
- All AEs and SAEs for patients who receive a treatment assignment code will be recorded in the eCRFs. During the active reporting period specified above, all AEs will be reported on the AE page(s) of the eCRF. It should be noted that the form for collection of SAE information is not the same as the AE eCRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the eCRFs as well as on the form for collection of SAE information.

- Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.
- Withdrawal due to AE should be distinguished from withdrawal due to insufficient response, according to the definition of AE noted earlier, and recorded on the appropriate AE eCRF page. In case of confirmed laboratory interferences, the initial AE should be replaced on the eCRF using the following verbatim "False [initial AE] due to laboratory interferences with laboratory test".

The information to be entered in the eCRF will include:

- The time of onset of any AE or the worsening of a previously observed AE
- The specific type of reaction in standard medical terminology
- The duration of the AE (start and stop dates)

3.3.1 Severity assessment

The severity of the adverse event (AE). The severity should be rated as:

- **Mild**: discomfort noted, but no disruption of normal daily activity.
- **Moderate**: discomfort noted of sufficient severity to reduce or adversely affect normal activity.
- **Severe**: incapacitating, with inability to work or perform normal daily activity.

3.3.2 Causality assessment

An assessment of the relationship of the adverse event (AE) to the study medication, i.e., according to the definitions below:

- **Definite**: a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The event must be pharmacologically or phenomenologically plausible, and its clinical response to withdrawal of the drug (dechallenge) should be clinically plausible. It must also be confirmed by a satisfactory rechallenge procedure.
- **Probable/likely**: a clinical event in which a relationship to the IP seems probable because of such factors as a clear temporal association with the use of the IP, lack of alternative explanations for the event or other factors.
- **Possible**: the essential distinctions between 'Probable' and 'Possible' are that in the latter case there may be another equally likely explanation for the event (could also be explained by disease or other drugs) and/or there is no information or uncertainty with regard to what has happened after stopping.
- **Unlikely**: a clinical event with a temporal relationship to IP administration that makes a causal relationship improbable and / or in which other factors suggesting an alternative aetiology exist. Such factors include a known relationship of the adverse event to concomitant drug, the patient's disease state or environmental factors including common infectious diseases.
- **Conditional/Unclassified**: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
- **Not related**: Not suspected to be reasonably related to the IP. A reasonable alternative explanation must be available.

In addition, if the investigator determines an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and eCRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

As far as possible, all investigators should follow-up participants with AEs until the event is resolved or until, in the opinion of the investigator, the event is stabilized or determined to be chronic. Details of AE resolution must be documented in the eCRF and in the source documents. Participants should be followed-up for 30 days after receiving the last dose of study medication and any AEs, which occur during this time, should be reported according to the procedures outlined above. Any significant changes in AEs should be reported even though the patient has completed the study, including the protocol-required post-treatment follow-up.

3.3.3 Assessment of seriousness

After the relationship, the **seriousness** shall be determined by the treating physician according to the definition given below:

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (SADR): Any untoward medical occurrence or effect that at any dose:

- Results in death
- Is life-threatening, (Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if more severe.)
- Requires hospitalization or prolongation of existing hospitalization
- Results in disability/incapacity
- Is a congenital anomaly/birth defect
- Medical or scientific judgment should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life threatening or result in death or hospitalization but may jeopardize the patient or may require medical or surgical intervention to prevent one of other outcomes listed in the above definition. These should also be considered serious.
- In this study, all MS relapses (as defined below) will be considered as a SAE. Study treatment should be maintained as much as possible.
    - All MS relapses (as defined below) reported by investigators will be recorded in an MS relapse form (annex 3) which will be communicated to and assessed by the Adjudication Committee for diagnosis validation and MEDDRA coding purpose.

3.4 Serious Adverse Events reporting

All SAEs and follow-up information must be reported to the sponsor on a SAE form within 24 hours of investigator awareness of the event.

All non-serious AE notified at the same time of serious AE shall be recorded and notified to the Pharmacovigilance unit of the sponsor.

The description of SAE will include a description of the AE with sufficient details to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to the Sponsor or its designated representative.

All adverse events encountered during the clinical study must be reported on the eCRF as soon as the data are available. Therefore, data will be accessible immediately by the sponsor or designee.

Serious adverse events (SAEs), whether or not associated with study medication administration, will be recorded both on the Adverse Event form of the eCRF and the SAE form (available from the eCRF web site or from the Investigator's study files).

ALL SAEs occurring during this study (from signature of informed consent) and up to 30 days after a patient discontinued or completed the study, whether or not related to the administration of study medications, must be reported by faxing the completed SAE form, after reviewing the report for consistency and accuracy within 24 hours of awareness by the investigator, to the e-mail address or fax number mentioned on the SAE reporting form (investigator site file).

As soon as new information is available, a follow-up SAE should be sent to PV immediately and the eCRF updated accordingly.

Medical Assistance

If there is a need to discuss any medical issues concerning a serious adverse event or to report a serious adverse event during the business hours, the sponsor can be contacted through the CRO medical monitor (contact details available in the investigator site file).

3.5 Sponsor Reporting Requirements to Regulatory Authority

Adverse event reporting, including suspected serious unexpected adverse reactions, will be carried out in accordance with applicable local regulations.

4 STATISTICAL CONSIDERATIONS

4.1 Determination of sample size

The sample size is determined in terms of superiority, between group 2 (MD1003 300 mg/day) versus group 1 (placebo) according to the primary endpoint, i.e. the proportion of patients with a clinical improvement defined as:

> "decreased EDSS at M12 confirmed at M15 (defined as a decrease of at least 1 point if initial EDSS from 3.5 to 5.5 and of at least 0.5 point if initial EDSS between 6 and 6.5) or with improved TW25 of at least 20% at M12 and M15 compared to the best EDSS and TW25 scores among inclusion and randomization visits"

In the previous MS-SPI study, the improvement percentage was 0% in the placebo group and 12.6% in the active arm.
For the sample size estimation of SPI2, hypotheses were set at 2% for the proportion of clinically improved patients in the placebo group and at 12% in the MD1003 group. These hypotheses lead to a power >90% with 600 patients.

4.2 Definition of populations for analysis

Safety population

All patients who receive at least one dose of study medication will be included in the safety analyses.

Intent-to-treat population (ITT)

All analyses will be performed according to the intent-to-treat principle, i.e. patients will be analysed according to the treatment arm they were assigned to by randomization. The ITT population will include all randomized patients.

Full Analyzable Set (FAS)

The FAS will include all randomized patients who:

- received at least one dose of study treatment
- and had at least one EDSS and TW25 assessment at visits V1/M-1 or V2/M0

- and had at least one post-baseline EDSS and TW25 assessment prior to study treatment discontinuation in the randomized double-blind study phase.

Per Protocol population (PP)

All patients of the ITT who receive at least one dose of study medication and with assessment of EDSS and TW25 at inclusion, randomization, V6/M12 and V7/M15, and without major protocol deviations.

Statistical analyses will be performed on the ITT, FAS and PP populations as delineated in the Statistical Analysis Plan.

General considerations

Planned analyses will be performed using SAS®, version 9.2 or later, SAS Institute, Cary, Northern Carolina, USA. Descriptive analyses will be performed. Data will be displayed graphically using histograms and boxplots and summarized as follows: continuous variables by descriptive statistics (number of patients [N], mean, standard deviation, minimum, median and maximum); categorical data by absolute and relative frequencies (n and %).

Quality assurance of the data and statistical analysis and the development of the statistical part of the study report will be made by the sponsor or designee.

All clinical data recorded as verbatim into the eCRF will be encoded in MedDRA last version.

4.2.1 Handling of Missing data

For the primary endpoint analysis, patients with missing data precluding evaluation will be considered non-responders.

For the secondary outcome measures, missing data will be adapted using the multiple imputation method derived from modelling the respective treatment arms. In sensitivity analyses the multiple imputation approach will be used where missing data will be conservatively imputed using the Gaussian distribution fitted on the available data of the placebo group at the same time point to that of missing data.

Details on imputation methods and sensitivity analyses concerning the main and the secondary endpoints will be fully described in the SAP of the study.

4.2.2 Multiplicity

No multiplicity adjustment is considered necessary for the primary endpoint as there is a unique main criterion and two arms to be compared; therefore, there is only one confirmatory hypothesis to be tested with an alpha risk of 5%.

However, secondary endpoints are hierarchically scaled by order of clinical importance and maintained to a few numbers in order to avoid multiplicity concerns.

4.3 **Efficacy evaluation**

4.3.1 Analysis of the primary endpoint

The main objective of the trial is to demonstrate the superiority of MD1003 over placebo on the progressive multiple sclerosis, comparing the proportion of patients with a clinical improvement between the MD1003 and placebo groups.

A logistic regression will be fitted to estimate the treatment effect (odd-ratio of improved patients) using treatment, disease history (SPMS/PPMS), geographical region, and center as fixed factors (referred as the main logistic model in the following parts).

Improvement is defined through the following composite outcome:

- Decreased EDSS at M12 confirmed at M15 (defined as a decrease of at least 1 point if initial EDSS from 3.5 to 5.5 and of at least 0.5 point if initial EDSS between 6 and 6.5) compared to the best EDSS obtained at either the inclusion or randomization visits

  or

- Improved TW25 of at least 20% at M12 and M15 compared to the best mean of the two TW25 mean scores obtained at either the inclusion or randomization visits.

It is required that in addition to overall statistical significance for the primary composite outcome, both elements of the composite outcome should be consistent with the overall outcome i.e. each component analysis must display a numerical advantage favouring the active arm. The numerical advantage does not have to demonstrate statistical significance with a p value < 0.05.

The main logistic model will then be used for each component of the composite outcome (EDSS and TW25 responses) to complement the main analysis of the main endpoint.

Sensitivity analyses of the main outcome will be further described in the SAP of the study, but they will particularly explore the potential influence of the following parameters on the estimate of the treatment effect:

- Subjects with and without relapses
- Subjects with and without steroid treatment during the study
- Subjects with and without modification of their disease modifying therapy

4.3.2 Analysis of secondary endpoints

1. Time to EDSS progression confirmed at 12 weeks (of at least 1 point if initial EDSS from 3.5 to 5.5 and of at least 0.5 point if initial EDSS from 6 to 6.5) will be graphically presented with survival curves. The median time to increase of EDSS and its 95% Confidence Interval in each treatment group, as well as the hazard ratio (test/control), will be estimated using a Cox-regression model using treatment and disease history (SPMS/PPMS) as well as region as fixed effects. A patient without progression performing his last double-blind evaluation of the study (after the last patient reaches Month 15 or Month 27, whichever comes first) will be censored at this date for the purpose of the analysis.
2. Comparison of CGI-I score (clinical global impression) at M15 evaluated both by the patient (SGI) and by the evaluating physician (CGI) will be performed using a Van Elteren test (stratified on disease history SPMS/PPMS).
3. Mean change in TW25 between M0 and M15 will be performed using a Van Elteren test (stratified on disease history SPMS/PPMS).

When applicable, the main endpoints will also be described and compared at M6, M9 and M12, to highlight a potential early effect of the treatment. Statistical analyses will be fully predefined in the SAP of the study

4.3.3 Analysis of exploratory endpoints

All pre-planned analyses will be described in detail within the Statistical Analysis Plan.

1. The brain MRI outcomes will be analysed between M0 and M15 (and between M0 and M27):
   - Mean percent thalamic volume change between M0 and M6, M0 and M15 (and between M0 and M27) will be performed using Mann-Whitney U test;
   - Mean percent brain volume change between M0 and M6, M0 and M15 (and between M0 and M27) will be performed using Mann-Whitney U test;
   - Mean percent cortical grey matter volume change between M0 and M6, M0 and M15 (and between M0 and M27) will be performed using Mann-Whitney U test;
   - Mean brain water content by Pseudo T2 relaxation time change between M0 and M6, M0 and M15 (and between M0 and M27) will be performed using Mann-Whitney U test;
   - Mean NAA/Cr change (in a subset of sites acquiring MRS) between M0 and M15 (and between M0 and M27) will be performed using Mann-Whitney U test.

2. Remote monitoring of ambulatory activity between M0 and M15 (and between M0 and M27 for patients on the double-blinded extension phase). Comparison of daily average step counts will be performed using Mann-Whitney U test. In addition, a MMRM (Mixed effect Model Repeat Measurement) will be performed as a sensitivity analysis
3. Mean change in the Multiple Sclerosis Quality of Life-54 (MSQOL-54) and in the Caregiver health-related quality of life in Multiple Sclerosis (CAREQOL-MS) subscores and composite scores between M0 and M15 (and between M0 and M27 for patients on the extension double-blinded phase) will be performed using Mann-Whitney U test.
4. Mean change in subscores of the Kurtzke functional score between M0 and M15 (and between M0 and M27 for patients on the extension double-blinded phase) will be performed using Mann-Whitney U test.
5. Mean change in Symbol Digit Modalities Test (SDMT) between M0 and M15 (and between M0 and M27 for patients on the extension double-blinded phase) will be performed using Mann-Whitney U test.

4.3.4 Active drug extension analysis

Patients on active drug in either Part 1 or Part 2 of the study will be followed principally for safety considerations. Efficacy measures such as EDSS and TW25 will be explored using descriptive statistics and time to major milestones.

4.4 **Safety evaluation**

The analysis will be based on the safety population and presented by treatment groups concerning the comparative phase of the study. An additional analysis will also describe the totality of the data of patients under active treatment. Safety analysis of Part 1 and Part 2 will be conducted in a similar fashion. More details are given in the study SAP.

<u>Study treatments exposure</u>

Exposure of treatments will be summarized for each period of the study (comparative/open).

<u>Adverse Events</u>

Adverse events will be summarized by presenting the number and percentage of patients having an adverse event, having an adverse event in each body system, and each individual adverse event.

Concomitant therapy

All concomitant medications taken during this study will be listed by patient.

Safety of MD1003 will be assessed by:

1. Recording of adverse events in the two groups: descriptive analyses will be performed.
2. Comparison of incidence of abnormal laboratory testing (haematology and biochemistry panel)
    a. CBC with differential
    b. Metabolic panel (fasting)
    c. Hepatic function panel
    d. Lipid panel (fasting)
    e. Thyroid panel
3. ECG

The assessment will be performed by the CSCL and include testing the effects on the QT/QTc interval. QTc interval will be calculated using Fridericia's correction: $QTc = QT/RR^{0.33}$
The QT/QTc interval data will be assessed both as analyses of central tendency (e.g., means, medians) and categorical analyses.
For central tendency, the effect of MD1003 on the QT/QTc interval will be analyzed using the largest time-matched mean difference between the drug and placebo (baseline-adjusted) over the collection period

For categorical analysis, QT/QTc interval data will be based on the number and percentage of patients meeting or exceeding some predefined upper limit values:

- Absolute QTc interval prolongation
    - QTc interval > 450
    - QTc interval > 480
    - QTc interval > 500
- Change from baseline in QTc interval:
    - QTc interval increases from baseline >30
    - QTc interval increases from baseline >60
- Statements regarding other ECG anomalies (rhythm, conduction and repolarization) and their change from baseline will be reported and analysed.

4. Brain MRI:

Analyses will be performed at each visit:

- Comparison of proportion of patients with at least one new/enlarging T2-weighted MS lesion (at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo): 95% Exact confidence intervals and Fisher's exact test.
- Mean number of new/enlarging T2-weighted MS lesions per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo): Mann-Whitney U test.
- Comparison of proportion of patients with at least one gadolinium enhancing lesion on the T1-weighted sequence at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo): 95% Exact confidence intervals and Fisher's exact test.
- Mean number of gadolinium enhancing lesions on the T1-weighted sequence at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo): Mann-Whitney U test.

- Mean number of new enlarging T2-weighted lesions per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo): Mann-Whitney U test.
- Mean of T2-weighted lesion volume per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo): Mann-Whitney U test.
- Mean of non-enhancing T1-weighted lesion volume per patient at M6 and M15 in group 2 (300 mg/day) versus group 1 (placebo): Mann-Whitney U test.

4.5 Interim analysis and data safety monitoring committee

No interim analysis is planned as part of this study.

The principal analysis is planned before the end of the entire trial, on the data collected during the double-blind 15-month phase.

In the extension phase of the study, the active study treatment will be dispensed in an open label fashion. Although the study treatment will be unblinded in the final months of the study, the study investigators, center staff and patients will remain masked to the prior randomized treatment assignments until the 27-month study has been completed.

DSMB can help sponsor and investigators of the study regarding decisions to be taken during the study for which independent judgment is desirable. DSMB may for this purpose:

- Recommend continue the study as planned
- recommend further analysis for the interpretation of the safety results;
- recommend minor or major modifications of the protocol based on safety issues and/or for the extension phase, made necessary because of the results of this principal analysis;
- recommend early termination of the trial for safety or efficacy reasons

4.6 Analysis by subgroups

Some analyses in subgroups, defined by the following factors, will be performed using forest-plots representation, in order to assess the homogeneity of treatment effect concerning the main endpoint and the 3 secondary endpoints:

- Region: North America/Australia vs Europe
- Disease history (SPMS/PPMS)
- EDSS at baseline: “3.5 to 5.5” vs “6 or above”
- Age
- Sex
- Disease duration
- Concomitant physical therapy
- BMI
- Use of concomitant Disease Modifying Therapies
- Use of concomitant myorelaxants

5 PRESTUDY DOCUMENTATION

The investigator must provide the sponsor with the following documents BEFORE enrolling any patients:

- Completed and signed statement of investigator form (i.e., FDA form 1572).

- All applicable country-specific regulatory forms.
- Current signed and dated curriculum vitae for the principal investigator, sub-investigators, determination of eligibility, efficacy, or safety) who are listed on the statement of investigator form (i.e., FDA form 1572).
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the subject must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) and, where required, a copy of the annual progress report submitted to the IRB/IEC must also be provided to the sponsor.
- Copy of the IRB/IEC-approved informed consent document to be used.
- If applicable, a list of the IRB/IEC members and their qualifications and a description of the committee's working procedure.
- Copy of the protocol sign-off page signed by the investigator.
- Fully executed Clinical Site Agreement.
- If applicable, a financial disclosure form.

6 INFORMED CONSENT

The investigator is responsible for the safety and protection of the patients by following all applicable regulations. These regulations are available upon request from the sponsor or designee. The informed consent document(s) used during the informed consent process must be reviewed by the sponsor, approved by the IRB/IEC, and available for inspection.

Before any protocol-required procedures are performed, a subject must:

- Be informed of all pertinent aspects of the study and elements of informed consent.
- Be given time to ask questions and time to consider the decision to participate.
- Voluntarily agree to participate in the study.
- Sign and date an IRB/IEC-approved informed consent document

The investigator must explain to each patient (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, in non-technical language. The subject should read and consider the statement before signing and dating it and should be given a copy of the signed document.

7 DIRECT ACCESS, DATA HANDLING AND RECORD-KEEPING

7.1 Investigator

The investigator will permit study-related monitoring, audits, IRB/IEC review, and regulatory inspections by providing direct access to source data and documents.

All information will be recorded on source documents. The eCRFs must be fully completed and include all required data. All eCRF data must be submitted to the sponsor throughout and at the end of the study. Remote data capture will be used to record and transmit data electronically to the sponsor or designee. The eCRF must be completed within 5 days after each visit.

If an investigator retires, relocates, or otherwise withdraws from conducting the study, the investigator must notify the sponsor to agree upon an acceptable storage solution. Regulatory agencies will be notified with the appropriate documentation. An updated statement of investigator form (i.e., US Food and Drug Administration [FDA] form 1572) will be filed with the sponsor or designee for any changes in the study personnel reported in the current statement of investigator form.

Investigators must notify their IRB/IEC of protocol violations in accordance with local regulatory and IRB/IEC requirements.

The investigator will allow the monitor to visit the site facilities where the study will take place in order to ensure that the site complies with the requirements of the protocol and the GCP.

7.2 Sponsor

The CRF data are stored in a database and processed electronically. The sponsor or designee reviews the data for safety information. The data are reviewed for legibility, completeness, and logical consistency. Automated validation programs identify missing data, out-of-range data, and other data inconsistencies. Requests for data clarification are forwarded to the investigative site for resolution.

At regular intervals during the study, the monitor will visit the site, to check the completeness of patients' records, the accuracy of entries on the eCRF, the adherence to protocol and to Good Clinical Practice, the progress of enrolment, and to ensure that study medication is being stored and accounted for according specifications.

The investigator and key trial personnel must be available to assists the monitor during these visits.

7.3 Source document requirements

The investigator must give the monitor direct access to relevant hospital or clinical records, to confirm their consistency with the eCRF data entries.

The consent form will include a statement by which the patients allows the sponsor's duly authorized personnel (trial monitoring team) to have **direct access** to source data which supports data on the electronic case report forms. These personnel, bound by professional secrecy, will not disclose any personal identity or personal medical information.

7.4 The use and completion of electronic Case Report Forms (eCRFs)

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs in recording all observations and other data pertinent to the clinical investigation on ongoing basis into the eCRFs designed by an eCRF provider.

1. CRFs are implemented electronically (eCRF), using third party software application that is fully validated and conforms to regulatory requirements for electronic data capture, where applicable.
2. The eCRF enables data capture via an on-line system on a personal computer (PC).

- Designated staff at participating sites shall enter data required by the protocol into the eCRF.
- All access to the system is administered by the eCRF administrator and will only be granted after appropriate and documented training. A dedicated account (with login and password) will be provided at each user by the eCRF administrator.
- Specific guidelines for data completion will be available.
- The data will be recorded via the application into a central database over encrypted lines using the SSL (Secure Sockets Layer) protocol.

- Personal health identifiers are stored in the central database in encrypted form.
- All entries and modifications of data are logged in an audit trail.
- Electronic signatures will be used where required.
- Automated validation program check for data discrepancies in the eCRFs will be implemented where appropriate.

8 ADMINISTRATIVE RULES

8.1 Curriculum vitae

An updated copy of the curriculum vitae of the investigator will be provided to the sponsor prior to the beginning of the study. An updated CV should be collected during the course of the study at least every 2 years.

8.2 Secrecy agreement

By signing the protocol, the investigator agrees to keep all information provided by the sponsor in strict confidence and to request similar confidentiality from his/her staff and the IRB/EC. Study documents provided by the sponsor will be stored appropriately to ensure their confidentiality.

The information provided by the sponsor to the investigator may not be disclosed to others without direct written authorization from the sponsor, except to the extent necessary to obtain informed consent from patients who wish to participate in the trial.

8.3 Protocol amendments

Any change in the study plan requires a protocol amendment. An investigator must not make any changes to the study without IRB/IEC and sponsor approval except when necessary to eliminate apparent immediate hazards to the patients. A protocol change intended to eliminate an apparent immediate hazard to patients may be implemented immediately, but the change must then be documented in an amendment, reported to the IRB/IEC within 5 working days, and submitted to the appropriate regulatory agency in the required time frame. All protocol amendments must be reviewed and approved by the sponsor and investigator.

8.4 Record retention in investigation center(s)

The investigator shall retain and preserve 1 copy of all data collected or databases generated in the course of the study, specifically including but not limited to those defined by GCP as essential, for the longer of (a) 2 years after the last marketing authorization for the study drug has been approved or the sponsor has discontinued its research with respect to such drug or (b) such longer period as required by applicable global regulatory requirements. At the end of such period, the investigator shall notify the sponsor in writing of his or her intent to destroy all such material. The sponsor shall have 30 days to respond to the investigator's notice, and the sponsor shall have a further opportunity to retain such materials at the sponsor's expense.

8.5 Insurance compensation

The sponsor certifies having taken out a liability insurance policy which covers the investigators and his co-workers and which is in accordance with the local laws and requirements.

A certificate of insurance will be provided to the investigator.

8.6 Quality control and assurance

The sponsor or designee performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any patients in this study, sponsor personnel or designee and the investigator review the protocol, the investigator's brochure, the eCRFs and instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and SAEs. A qualified representative of the sponsor will monitor the conduct of the study. During these site visits, information recorded in the eCRFs is verified against source documents.

8.7 Ownership of results - Publication

The results from this study are the exclusive property of the sponsor.

No information concerning the study, or its results may be published or communicated without the prior written and signed agreement of the sponsor.

The sponsor's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and sponsor policies regarding publication and communication of clinical study results.

8.8 Study Specific Committees

8.8.1 Scientific and Steering committee

Members:

- Prof. Fred LUBLIN, New York, USA (Chairman);
- Prof. Bruce CREE, San Francisco, USA;
- Prof Gary CUTTER, Birmingham, USA;
- Prof Jerry WOLINSKY, Houston, USA;
- Prof. Mark FREEDMAN, Ottawa, Canada;
- Prof. Giancarlo COMI, Milan, Italy;
- Prof. Gavin GIOVANNONI, London, UK;
- Prof. Hans-Peter HARTUNG, Düsseldorf, Germany

***Missions*:**

- Defining the study objective, designing the study protocol, and proposing protocol amendments during the study.
- Defining the general organization, maintaining the quality of study conduct,
- Analysing the information provided by the Adjudication Committee (AC) and the Data Safety Monitoring Board (DSMB),
- Ongoing monitoring of individual toxicities and adverse events,
- Writing study publications

8.8.2 Adjudication Committee

For independent adjudication, members are not involved at all as investigators, sub-investigators or any tasks related to the recruitment in the SPI2 clinical trial.

Members:

- Prof. Robert P. LISAK, Detroit, USA (Chairman);
- Dr. Jennifer GRAVES, San Francisco, USA;
- Dr. Stephen KRIEGER, New York, USA;
- Dr. Rana K. ZABAD, Omaha, USA;
- Dr. Scott NEWSOME, Baltimore, USA.

***Missions*:**

- To validate eligibility of patients especially regarding the documentation of disease progression prior inclusion.
- To analyse relapsing episodes and categorize these AEs as per protocol definitions (§ 3.2).

8.8.3 Data Safety Monitoring Board (DSMB)

DSMB is an independent advisory committee. It will be set-up and managed by the CRO.

Members:

- Prof. Stephen REINGOLD, Salisbury, USA;
- Prof. Pierre DUQUETTE, Montreal, Canada;
- Prof. Tobias DERFUSS, Basel, Switzerland;
- Prof. Franz FAZEKAS, Graz, Austria;
- Prof. Maria Pia SORMANI, Genoa, Italy

Missions

- To ensure patients safety and rights throughout the study,
- To preserve the scientific and ethical integrity of the study.
- To provide the sponsor with recommendations on the conduct of the study.
- To help sponsor and investigators regarding decisions to be taken during the study when independent judgment is desirable, such as:
  - recommend further analysis to the interpretation of the results of an interim review of data
  - recommend minor or major modifications of the protocol became necessary because of recruitment, or follow-up testing or, to take account of new scientific data
  - recommend early termination of the trial.
- To advise on the continuation of the trial in case of SUSARs.

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10 APPENDICES

Annex 1: Revised Mc Donald criteria

National Multiple Sclerosis Society

TipSheet

ECTRIMS EUROPEAN COMMITTEE FOR TREATMENT AND RESEARCH IN MULTIPLE SCLEROSIS

2010 Revised McDonald Diagnostic Criteria for MS[1]

Diagnosis of MS requires elimination of more likely diagnoses and demonstration of dissemination of lesions in space and time

CLINICAL (ATTACKS)	LESIONS	ADDITIONAL CRITERIA TO MAKE DX
2 or more	Objective clinical evidence of 2 or more lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack	None. Clinical evidence alone will suffice; additional evidence desirable but must be consistent with MS
2 or more	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by ➢ ≥ 1T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratorial, spinal cord); **OR** ➢ Await further clinical attack implicating a different CNS site
1	Objective clinical evidence of 2 or more lesions	Dissemination in time, demonstrated by ➢ Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time ; **OR** ➢ A new T2 and/or contrast-enhancing lesions(s) on follow-up MRI, irrespective of its timing; **OR** ➢ Await a second clinical attack
1	Objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by ➢ ≥ 1T2 lesion in at least two MS typical CNS regions (periventricular, juxtacortical, infratentorial, spinal cord); **OR** ➢ Await further clinical attack implicating a different CNS site **AND** Dissemination in time, demonstrated by ➢ Simultaneous asymptomatic contrast-enhancing and non-enhancing lesions at any time; **OR** ➢ A new T2 and/or contrast-enhancing lesions(s) on follow-up MIR, irrespective of its timing; **OR** ➢ Await a second clinical attack
0 (progression from onset)		One year of disease progression (retrospective or prospective) **AND** at least 2 out of 3 criteria: ➢ Dissemination in space in the brain based on ≥1 T2 lesion in periventricular, juxtacortical or infratentorial regions; ➢ Dissemination in space in the spinal cord based on ≥2 T2 lesions; **OR** ➢ Positive CSF

[1]Polman C et al. *Annals of Neurology* (2011;69:292-302) http://onlinelibrary.wiley.com/doi/10.1002/ana.22366/abstract

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Annex 2: Neurostatus

EQUIVALENCE WITH PREVIOUS VERSIONS

This version of the neurostatus scoring guidelines is fully compatible with previous versions. Additional help is provided by clarifying some definitions and by introducing an ambulation score in order to reduce measurement noise. But these changes do not imply changes in scoring levels.

GENERAL GUIDELINES

To ensure unbiased EDSS assessment in controlled clinical trials, the EDSS rater should not inquire about the patients' condition except as necessary to perform the EDSS assessment. Patients must be observed to walk the required distance.
The functional system and EDSS scores should reflect the MS related deficits only. In case of doubt the examining physician should assume a relation to MS.
Temporary signs or symptoms that are not due to multiple sclerosis, e.g. temporal immobilisation after fracture of one limb, as well as permanent signs or symptoms that are not due to multiple sclerosis, e.g leg amputation after accident, will not be taken into consideration when assessing the FS scores and EDSS steps, but need to be noted in neurostatus and commented by adding "P" next to the respective field on the scoring sheet for permanent findings and "T" for temporary findings.

FUNCTIONAL SYSTEMS (FS)

A neurostatus score "signs only" is noted when the examination reveals signs of which the patient is unaware.
A score of 1 in a Functional System implies that the patient is not aware of the deficit and that the deficit or sign does not interfere with normal daily activities. However, this general rule does not apply to the Visual, Bowel/Bladder and Cerebral FS.

EXPANDED DISABILITY STATUS SCALE (EDSS)

The EDSS step should not be lower than the score of any individual FS, with the exception of the Visual and Bowel/Bladder FS before conversion.

EDSS steps from 0 up to 4.0 should not change compared to the previous examination, unless there is a change by one grade in at least one FS score.
EDSS steps from 0 up to 1.5 can only apply if ambulation is "unrestricted".
EDSS steps from 2.0 up to 5.0 are defined by the Functional System (FS) scores and/or walking range restriction. As an example, EDSS step 5.0 is possible with an unrestricted ambulation. EDSS steps from 2.0 up to 4.0 does only apply in individuals when at least "fully ambulatory" (able to walk ≥500 meters). If ambulation is assessed as "restricted" the pyramidal or cerebellar FS must be ≥2.
EDSS steps ≥ 5.5 are exclusively defined by the ability to ambulate, the assistance required or the use of a wheelchair.

1 VISUAL (OPTIC) FUNCTIONS

VISUAL ACUITY

The visual acuity score is based on the line in the Snellen chart at 20 feet (5 meters) for which the patient makes no more than one error, using best available correction. Alternatively, best corrected near vision can be assessed, but this should be noted and consistently performed during follow-up examinations. Switching from near to distance visual acuity measurements should be avoided in follow-up examinations.

VISUAL FIELDS

0 normal
1 signs only: deficits present only on formal (confrontational) testing
2 moderate: patient aware of deficit, but incomplete hemianopsia on examination
3 marked: complete homonymous hemianopsia or equivalent

SCOTOMA

0 none
1 small: detectable only on formal (confrontational) testing
2 large: spontaneously reported by patient

*DISC PALLOR

0 not present
1 present

NOTE

When determining the EDSS step, the Visual FS score must be converted to a lower score as follows:

Visual FS Score	6	5	4	3	2	1
Converted Visual FS Score	4	3	3	2	2	1

FUNCTIONAL SYSTEM SCORE

0 normal
1 disc pallor and/or small scotoma and/or visual acuity (corrected) of worse eye less than 20/20 (1.0) but better than 20/30 (0.67)
2 worse eye with maximal visual acuity (corrected) of 20/30 to 20/59 (0.67–0.34)
3 worse eye with large scotoma and/or moderate decrease in fields and/or maximal visual acuity (corrected) of 20/60 to 20/99 (0.33–0.21)
4 worse eye with marked decrease of fields and/or maximal visual acuity (corrected) of 20/100 to 20/200 (0.2–0.1);
grade 3 plus maximal acuity of better eye of 20/60 (0.33) or less
5 worse eye with maximal visual acuity (corrected) less than 20/200 (0.1);
grade 4 plus maximal acuity of better eye of 20/60 (0.33) or less
6 grade 5 plus maximal visual acuity of better eye of 20/60 (0.33) or less

* = optional part of the examination.

2 BRAINSTEM FUNCTIONS

EXTRAOCULAR MOVEMENTS (EOM) IMPAIRMENT

0 none
1 signs only: subtle and barely clinically detectable EOM weakness, patient does not complain of blurry vision, diplopia or discomfort
2 mild: subtle and barely clinically detectable EOM weakness of which patient is aware; or obvious incomplete paralysis of any eye movement of which patient is not aware
3 moderate: obvious incomplete paralysis of any eye movement of which patient is aware; or complete loss of movement in one direction of gaze in either eye
4 marked: complete loss of movement in more than one direction of gaze in either eye

NYSTAGMUS

0 none
1 signs only or mild: gaze evoked nystagmus below the limits of "moderate" (equivalent to a Brainstem FS score of 1)
2 moderate: sustained nystagmus on horizontal or vertical gaze at 30 degrees, but not in primary position, patient may or may not be aware of the disturbance
3 severe: sustained nystagmus in primary position or coarse persistent nystagmus in any direction that interferes with visual acuity; complete internuclear ophthalmoplegia with sustained nystagmus of the abducting eye; oscillopsia

TRIGEMINAL DAMAGE

0 none
1 signs only
2 mild: clinically detectable numbness of which patient is aware
3 moderate: impaired discrimination of sharp/dull in one, two or three trigeminal branches; trigeminal neuralgia (at least one attack in the last 24 hours)
4 marked: unable to discriminate between sharp/dull or complete loss of sensation in entire distribution of one or both trigeminal nerves

FACIAL WEAKNESS

0 none
1 signs only
2 mild: clinically detectable facial weakness of which patient is aware
3 moderate: incomplete facial palsy, such as weakness of eye closure that requires patching overnight or weakness of mouth closure that results in drooling
4 marked: complete unilateral or bilateral facial palsy with lagophthalmus or difficulty with liquids

HEARING LOSS

0 none
1 signs only: hears finger rub less in one or both sides and has lateralized Weber test but does not complain of any hearing problem
2 mild: as in 1 but is aware of hearing problem
3 moderate: does not hear finger rub on one or both sides, misses several whispered numbers
4 marked: misses all or nearly all whispered numbers

DYSARTHRIA

0 none
1 signs only
2 mild: clinically detectable dysarthria of which patient is aware
3 moderate: obv. dysarthria during ordinary conversation that impairs comprehensibility
4 marked: incomprehensible speech
5 inability to speak

DYSPHAGIA

0 none
1 signs only
2 mild: difficulty with thin liquids
3 moderate: difficulty with liquids and solid food
4 marked: sustained difficulty with swallowing; requires a pureed diet
5 inability to swallow

OTHER CRANIAL NERVE FUNCTIONS

0 normal
1 signs only
2 mild disability: clinically detectable deficit of which patient is usually aware
3 moderate disability
4 marked disability

FUNCTIONAL SYSTEM SCORE

0 normal
1 signs only
2 moderate nystagmus and/or moderate EOM impairment and/or other mild disability
3 severe nystagmus and/or marked EOM impairment and/or moderate disability of other cranial nerves
4 marked dysarthria and/or other marked disability
5 inability to swallow or speak

3 PYRAMIDAL FUNCTIONS

REFLEXES

0 absent
1 diminished
2 normal
3 exaggerated
4 nonsustained clonus (a few beats of clonus)
5 sustained clonus

Cutaneous Reflexes
0 normal
1 weak
2 absent

*Palmomental Reflex
0 absent
1 present

Plantar Response
0 flexor
1 neutral or equivocal
2 extensor

LIMB STRENGTH

The weakest muscle in each group defines the score for that muscle group. Use of optional functional tests (hopping on one foot and walking on heels/toes), is highly recommended in order to assess BMRC grades 3–5.

BMRC RATING SCALE

0 no muscle contraction detected
1 visible contraction without visible joint movement
2 visible movement only on the plane of gravity
3 active movement against gravity, but not against resistance
4 active movement against resistance, but not full strength
5 normal strength

FUNCTIONAL TESTS

*Pronator Drift (upper extremities) Pronation and downward drift:
0 none
1 mild
2 evident

*Position Test (lower extremities – ask patient to lift both legs together, with legs fully extended at the knee) Sinking:
0 none
1 mild
2 evident
3 able to lift only one leg at a time (grade from the horizontal pos. at the hip joints…°)
4 unable to lift one leg at a time

*Walking on heels/toes
0 normal
1 impaired
2 not possible

*Hopping on one foot
0 normal
1 6–10 times
2 1–5 times
3 not possible

LIMB SPASTICITY (AFTER RAPID FLEXION OF THE EXTREMITY)

0 none
1 mild: barely increased muscle tone
2 moderate: moderately increased muscle tone that can be overcome and full range of motion is possible
3 severe: severely increased muscle tone that is extremely difficult to overcome and full range of motion is not possible
4 contracted

GAIT SPASTICITY

0 none
1 barely perceptible
2 evident: minor interference with function
3 permanent shuffling: major interference with function

OVERALL MOTOR PERFORMANCE

0 normal
1 abnormal weakness (as compared to peers) in performing more demanding tasks, e.g. when walking longer distances, but no reduction in limb strength on formal (confrontational) testing
2 Reduction in strength of individual muscle groups at confrontational testing

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 minimal disability: patient complains of motor-fatigability or reduced performance in strenuous motor tasks (motor performance grade 1) and/or BMRC grade 4 in one or two muscle groups
3 mild to moderate paraparesis or hemiparesis: usually BMRC grade 4 in more than two muscle groups;
and/or BMRC grade 3 in one or two muscle groups (movements against gravity are possible);
and/or severe monoparesis: BMRC grade 2 or less in one muscle group
4 marked paraparesis or hemiparesis: usually BMRC grade 2 in two limbs or monoplegia with BMRC grade 0 or 1 in one limb;
and/or moderate tetraparesis: BMRC grade 3 in three or more limbs
5 paraplegia: BMRC grade 0 or 1 in all muscle groups of the lower limbs;
and/or marked tetraparesis: BMRC grade 2 or less in three or more limbs;
and/or hemiplegia;
6 tetraplegia: BMRC grade 0 or 1 in all muscle groups of the upper and lower limbs

4 CEREBELLAR FUNCTIONS

HEAD TREMOR

0 none
1 mild
2 moderate
3 severe

TRUNCAL ATAXIA

0 none
1 signs only
2 mild: swaying with eyes closed
3 moderate: swaying with eyes open
4 severe: unable to sit without assistance

LIMB ATAXIA (TREMOR/DYSMETRIA AND RAPID ALTERNATING MOVEMENTS)

0 none
1 signs only
2 mild: tremor or clumsy movements easily seen, minor interference with function
3 moderate: tremor or clumsy movements interfere with function in all spheres
4 severe: most functions are very difficult

TANDEM (STRAIGHT LINE) WALKING

0 normal
1 impaired
2 not possible

GAIT ATAXIA

0 none
1 signs only
2 mild: problems with balance realized by patient and/or significant other
3 moderate: abnormal balance with ordinary walking
4 severe: unable to walk more than a few steps unassisted or requires a walking aid or assistance by another person because of ataxia

ROMBERG TEST

0 normal
1 mild: mild instability with eyes closed
2 moderate: not stable with eyes closed
3 severe: not stable with eyes open

OTHER CEREBELLAR TESTS

0 normal
1 mild abnormality
2 moderate abnormality
3 severe abnormality

NOTE

The presence of severe gait and/or truncal ataxia alone (without severe ataxia in three or four limbs) results in a Cerebellar FS score of 3.
If weakness or sensory deficits interfere with the testing of ataxia, score the patient's actual performance. To indicate the possible role of weakness make an "X" after the affected subsystems and Cerebellar FS score.

FUNCTIONAL SYSTEM SCORE

0 normal
1 abnormal signs without disability
2 mild ataxia and/or moderate station ataxia (Romberg) and/or tandem walking not possible
3 moderate limb ataxia and/or moderate or severe gait/truncal ataxia
4 severe gait/truncal ataxia and severe ataxia in three or four limbs
5 unable to perform coordinated movements due to ataxia
X pyramidal weakness (BMRC grade 3 or worse in limb strength) or sensory deficits interfere with cerebellar testing

5 SENSORY FUNCTIONS

SUPERFICIAL SENSATION (LIGHT TOUCH AND PAIN)

0 normal
1 signs only: slightly diminished sensation (temperature, figure-writing) on formal testing of which patient is not aware
2 mild: patient is aware of impaired light touch or pain, but is able to discriminate sharp/dull
3 moderate: impaired discrimination of sharp/dull
4 marked: unable to discriminate between sharp/dull and/or unable to feel light touch
5 complete loss: anaesthesia

VIBRATION SENSE (AT THE MOST DISTAL JOINT)

0 normal
1 mild: graded tuning fork 5–7 of 8; alternatively, detects more than 10 seconds but less than the examiner
2 moderate: graded tuning fork 1–4 of 8; alternatively, detects between 2 and 10 sec.
3 marked: complete loss of vibration sense

POSITION SENSE

0 normal
1 mild: 1–2 incorrect responses, only distal joints affected
2 moderate: misses many movements of fingers or toes; proximal joints affected
3 marked: no perception of movement, astasia

*LHERMITTE'S SIGN

Does not contribute to the Sensory FS score
0 negative
1 positive

*PARAESTHESIAE (TINGLING)

Does not contribute to the Sensory FS score
0 none
1 present

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild vibration or figure-writing or temperature decrease only in one or two limbs
2 mild decrease in touch or pain or position sense or moderate decrease in vibration in one or two limbs;
and/or mild vibration or figure-writing or temperature decrease alone in more than two limbs
3 moderate decrease in touch or pain or position sense or marked reduction of vibration in one or two limbs;
and/or mild decrease in touch or pain or moderate decrease in all proprioceptive tests in more than two limbs
4 marked decrease in touch or pain in one or two limbs;
and/or moderate decrease in touch or pain and/or marked reduction of proprioception in more than two limbs
5 loss (essentially) of sensation in one or two limbs;
and/or moderate decrease in touch or pain and/or marked reduction of proprioception for most of the body below the head
6 sensation essentially lost below the head

6 BOWEL AND BLADDER FUNCTIONS

URINARY HESITANCY AND RETENTION

0 none
1 mild: no major impact on lifestyle
2 moderate: urinary retention; frequent urinary tract infections
3 severe: requires catheterisation
4 loss of function: overflow incontinence

URINARY URGENCY AND INCONTINENCE

0 none
1 mild: no major impact on lifestyle
2 moderate: rare incontinence occurring no more than once a week; must wear pads
3 severe: frequent incontinence occurring from several times a week to more than once a day; must wear urinal or pads
4 loss of function: loss of bladder control

BLADDER CATHETERISATION

0 none
1 intermittent self-catheterisation
2 constant catheterisation

BOWEL DYSFUNCTION

0 none
1 mild: no incontinence, no major impact on lifestyle, mild constipation
2 moderate: must wear pads or alter lifestyle to be near lavatory
3 severe: in need of enemata or manual measures to evacuate bowels
4 complete loss of function

*SEXUAL DYSFUNCTION

Male

0 none
1 mild: difficulty to maintain erection during intercourse, but achieves erection and still has intercourse
2 moderate: difficulty to achieve erection, decrease in libido, still has intercourse and reaches orgasm
3 severe: marked decrease in libido, inability to achieve full erection, intercourse with difficulty and hypoorgasmia
4 loss of function

Female

0 none
1 mild: mild lack of lubrication, still sexually active and reaches orgasm
2 moderate: dysparunia, hypoorgasmia, decrease in sexual activity
3 severe: marked decrease in sexual activity, anorgasmia
4 loss of function

NOTE

When determining the EDSS step, the Bowel and Bladder FS score must be converted to a lower score as follows:

Bowel and Bladder FS Score	6	5	4	3	2	1
Converted Bowel and Bladder FS Score	5	4	3	3	2	1

Sexual dysfunction can be documented but in general does not impact on FS score because of obvious difficulties in assessment by examining physician

FUNCTIONAL SYSTEM SCORE

0 normal
1 mild urinary hesitancy, urgency and/or constipation
2 moderate urinary hesitancy/retention and/or moderate urinary urgency/incontinence and/or moderate bowel disfunction
3 frequent urinary incontinence or intermittent self-catheterisation; needs enemata or manual measures to evacuate bowels
4 in need of almost constant catheterisation
5 loss of bladder or bowel function; external or indwelling catheter
6 loss of bowel and bladder function

7 CEREBRAL FUNCTIONS

° DEPRESSION AND EUPHORIA

0 none
1 present: Patient complains of depression or is considered depressed or euphoric by the investigator or significant other.

° Depression and Euphoria are documented on the scoring sheet but are not taken into consideration for FS and EDSS calculation.

DECREASE IN MENTATION

0 none
1 signs only: not apparent to patient and/or significant other
2 mild: Patient and/or significant other report mild changes in mentation. Examples include: impaired ability to follow a rapid course of association and in surveying complex matters; impaired judgement in certain demanding situations; capable of handling routine daily activities, but unable to tolerate additional stressors; intermittently symptomatic even to normal levels of stress; reduced performance; tendency toward negligence due to obliviousness or fatigue.
3 moderate: definite abnormalities on brief mental status testing, but still oriented to person, place and time
4 marked: not oriented in one or two spheres (person, place or time), marked effect on lifestyle
5 dementia, confusion and/or complete disorientation

+FATIGUE

0 none
1 mild: does not usually interfere with daily activities
2 moderate: interferes, but does not limit daily activities for more than 50 %
3 severe: significant limitation in daily activities (> 50 % reduction)

+Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

FUNCTIONAL SYSTEM SCORE

0 normal
1 signs only in decrease in mentation; mild fatigue
2 mild decrease in mentation; moderate or severe fatigue
3 moderate decrease in mentation
4 marked decrease in mentation
5 dementia

8 AMBULATION

Unrestricted ambulation means the patient is able to walk a distance without assistance that is regarded as normal, compared with healthy individuals of similar age and physical condition. In this case the EDSS step can be anything between 0 and 5.0, depending on the FS scores.

Fully ambulatory means at least 500 meters of ambulation without assistance, but not unrestricted. The EDSS step can be anything between 2.0 and 5.0, depending on the FS scores. In this case, the pyramidal and/or cerebellar FS must be ≥2 to reflect this „restriction" of ambulation.

If ambulation is < 500 meters, the EDSS step must be ≥ 4.5 depending on the walking ranges provided by the ambulation score (see next page) and combination of FS scores. EDSS steps 5.5 to 8.0 are exclusively defined by the ability to ambulate and type of assistance required, or the ability to use a wheelchair.

If assistance is needed, the definitions of EDSS steps 6.0 or 6.5 include both a description of the type of assistance required when walking and the walking range. Assistance by another person is equivalent to bilateral assistance.

NOTE

The ambulation score represents both a description of walking range and the type of assistance required for ambulation. The score replaces the former use of several checkboxes (paragraph 8 ambulation on the scoring sheet) but does NOT introduce new definitions. The use of wheelchair can now be scored on the scoring sheet.
Please indicate the reported distance and time for the patient in the appropriate field on the scoring sheet, followed by the type of assistance and the walking distance measured during the assessment.

DISTANCE AND TIME REPORTED BY PATIENT

Maximal unassisted walking distance reported by patient (in meters) without rest or assistance and time required to walk max. distance according to patient (in minutes)

ASSISTANCE

0 Without help or assistance (allowing the use of an ankle foot orthotic device, without any other type of assistive device)
1 Unilateral assistance: one stick/crutch/brace
2 Bilateral assistance: two sticks/crutches/braces or assistance by another person
3 Wheelchair

DISTANCE

Measure the distance the patient is able to walk im meters.
Unassisted: observe the patient walking unassisted for a minimum distance of 500 meters and measure the time needed, if possible.
Assisted: observe the patient walking with the assistive device or help by another person for a minimum distance of 130 meters, if possible.

AMBULATION SCORE

0 Unrestricted
1 Fully ambulatory
2 ≥ 300 meters, but < 500 meters, without help or assistance (EDSS 4.5 or 5.0)
3 ≥ 200 meters, but < 300 meters, without help or assistance (EDSS 5.0)
4 ≥ 100 meters, but < 200 meters, without help or assistance (EDSS 5.5)
5 Walking range < 100 meters without assistance (EDSS 6.0)
6 unilateral assistance, ≥ 50 meters (EDSS 6.0)
7 bilateral assistance, ≥ 120 meters (EDSS 6.0)
8 unilateral assistance, < 50 meters (EDSS 6.5)
9 bilateral assistance, ≥ 5 meters, but < 120 meters (EDSS 6.5)
10 Uses wheelchair without help; unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day (EDSS 7.0)
11 Uses wheelchair with help; unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self (EDSS 7.5)
12 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms (EDSS 8.0)

9 EXPANDED DISABILITY STATUS SCALE

0 normal neurological exam (all FS grade 0)
1.0 no disability, minimal signs in one FS (one FS grade 1)
1.5 no disability, minimal signs in more than one FS (more than one FS grade 1)
2.0 minimal disability in one FS (one FS grade 2, others 0 or 1)
2.5 minimal disability in two FS (two FS grade 2, others 0 or 1)
3.0 moderate disability in one FS (one FS grade 3, others 0 or 1) though fully ambulatory; or mild disability in three or four FS (three/four FS grade 2, others 0 or 1) though fully ambulatory
3.5 fully ambulatory but with moderate disability in one FS (one FS grade 3) and mild disability in one or two FS (one/two FS grade 2) and others 0 or 1; or fully ambulatory with two FS grade 3 (others 0 or 1);or fully ambulatory with five FS grade 2 (others 0 or 1)
4.0 ambulatory without aid or rest for ≥500 meters; up and about some 12 hours a day despite relatively severe disability consisting of one FS grade 4 (others 0 or 1) or combinations of lesser grades exceeding limits of previous steps
4.5 ambulatory without aid or rest for ≥300 meters; up and about much of the day, characterised by relatively severe disability usually consisting of one FS grade 4 and combination of lesser grades exceeding limits of previous steps
5.0 ambulatory without aid or rest for ≥200 meters (usual FS equivalents include at least one FS grade 5, or combinations of lesser grades usually exceeding specifications for step 4.5)
5.5 ambulatory without aid or rest for ≥100 meters
6.0 unilateral assistance (cane or crutch) required to walk at least 100 meters with or without resting (see chapter 8, Ambulation)
6.5 constant bilateral assistance (canes or crutches) required to walk at least 20 meters without resting (see chapter 8, Ambulation)
7.0 unable to walk 5 meters even with aid, essentially restricted to wheelchair; wheels self and transfers alone; up and about in wheelchair some 12 hours a day
7.5 unable to take more than a few steps; restricted to wheelchair; may need some help in transferring and in wheeling self
8.0 essentially restricted to bed or chair or perambulated in wheelchair, but out of bed most of day; retains many self-care functions; generally has effective use of arms
8.5 essentially restricted to bed much of the day; has some effective use of arm(s); retains some self-care functions
9.0 helpless bed patient; can communicate and eat
9.5 totally helpless bed patient; unable to communicate effectively or eat/swallow
10 death due to MS

neurostatus scoring

Scoring Sheet for a standardised, quantified neurological examination and assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale in Multiple Sclerosis

STUDY NAME

PERSONAL INFORMATION

Patient	
Date of Birth (04-Jun-1980)	__-___-____
Centre Nr/Country	
Name of EDSS rater	
Date of Examination	__-___-20__

SYNOPSIS

1. Visual	[1]	Ambulation Score	
2. Brainstem			
3. Pyramidal		EDSS Step	
4. Cerebellar			
5. Sensory			
6. Bowel/Bladder	[1]	Signature	
7. Cerebral			

1. VISUAL (OPTIC) FUNCTIONS

OPTIC FUNCTIONS	OD	OS
Visual acuity ☐ CC ☐ SC		
Visual fields		

Scotoma		
* Disc pallor		
FUNCTIONAL SYSTEM SCORE	→	[1]

2. BRAINSTEM FUNCTIONS

CRANIAL NERVE EXAMINATION	
Extraocular movements (EOM) impairment	
Nystagmus	
Trigeminal damage	
Facial weakness	

Hearing loss	
Dysarthria	
Dysphagia	
Other cranial nerve functions	
FUNCTIONAL SYSTEM SCORE	

3. PYRAMIDAL FUNCTIONS

REFLEXES	R	><	L
Biceps			
Triceps			
Brachioradialis			
Knee			
Ankle			
Plantar response			
Cutaneous reflexes			
* Palmomental reflex			

LIMB STRENGTH	R	L
Deltoid		
Biceps		
Triceps		
Wrist/finger flexors		
Wrist/finger extensors		
Hip flexors		
Knee flexors		

Knee extensors		
Plantar flexion (feet/toes)		
Dorsiflexion (feet/toes)		
* Position test UE, pronation		
* Position test UE, downward drift		
* Position test LE, sinking		
* Able to lift only one leg at a time (grade in °)	°	°
* Walking on heels		
* Walking on toes		
* Hopping on one foot		
SPASTICITY		
Arms		
Legs		
Gait		
OVERALL MOTOR PERFORMANCE		
FUNCTIONAL SYSTEM SCORE		

CC = corrected
SC = without correction
* = optional part of the examination
[1] = converted FS Score

4. CEREBELLAR FUNCTIONS

CEREBELLAR EXAMINATION	R	L
Head tremor		
Truncal ataxia		
Tremor/dysmetria UE		
Tremor/dysmetria LE		

Rapid alternating movements UE impairment		
Rapid alternating movements LE impairment		
Tandem walking		
Gait ataxia		
Romberg test		
Other, e. g. rebound		
FUNCTIONAL SYSTEM SCORE		

5. SENSORY FUNCTIONS

SENSORY EXAMINATION	R	L
Superficial sensation UE		
Superficial sensation trunk		
Superficial sensation LE		
Vibration sense UE		
Vibration sense LE		

Position sense UE		
Position sense LE		
* Lhermitte's sign		
* Paraesthesiae UE		
* Paraesthesiae trunk		
* Paraesthesiae LE		
FUNCTIONAL SYSTEM SCORE		

6. BOWEL/ BLADDER FUNCTIONS

Urinary hesitancy/retention		Bowel dysfunction	
Urinary urgency/incontinence		* Sexual dysfunction	
Bladder catheterisation		FUNCTIONAL SYSTEM SCORE →	[1]

7. CEREBRAL FUNCTIONS

MENTAL STATUS EXAMINATION			
° Depression		° Fatigue	
° Euphoria		FUNCTIONAL SYSTEM SCORE	

Decrease in mentation			

AMBULATION

Distance reported by patient (in meters)		Assistance	
Time reported by patient (in minutes)		Distance measured (in meters)	
		AMBULATION SCORE	

* = optional part of the examination
[1] = converted FS Score
° Depression and Euphoria are not taken into consideration for FS and EDSS calculation.
* Because fatigue is difficult to evaluate objectively, in some studies it does not contribute to the Cerebral FS score or EDSS step. Please adhere to the study's specific instructions.

UE = upper extremities
LE = lower extremities

Standardised Neurological Examination and Assessment of Kurtzke's Functional Systems and Expanded Disability Status Scale
Slightly modified from J.F. Kurtzke, Neurology 1983:33,1444-52

Annex 3: Relapse assessment questionnaire

Visit Date : __/__/____ (MM DD YYYY) Patient N°|__|__|__| |__|__|__|

SPI2 Relapse Assessment questionnaire

Visit:

❑ Randomization M0	❑ Visit M3	❑ Visit M6	❑ Visit M9
❑ Visit M12	❑ Visit M15	❑ Visit M18	❑ Visit M21
❑ Visit M24	❑ Visit M27	❑ Visit M30	❑ Visit M36
❑ Visit M42	❑ Visit M48	❑ Visit M54	❑ Visit M60
❑ Final Visit M66	❑ Unscheduled Visit	❑ Early Termination Visit	

This form is for symptoms related to Multiple Sclerosis.
If the subject is experiencing symptoms NOT due to MS, please use AE section.

To be filled out by the Treating Physician

1. Is the subject having new neurologic symptom(s) or an acute worsening of preexisting neurologic symptom(s) related to MS?

❑ No → IF NO – STOP Form, the subject has not experienced a relapse.

❑ Yes → IF YES, date of onset: __/__/____ (MM DD YYYY)

If date of onset is today then SKIP to Question 2, otherwise continue to 1a

1a. Did the symptoms last more than 24 hours?
- ❑ Yes **Continue to Question 2**
- ❑ No **STOP – Not a protocol relapse SKIP to Question 8, page 2**

2. Does/Did the subject have a fever due to intercurrent illness?

❑ Yes → IF YES – STOP Skip to Question 8, page 2

❑ No → IF NO – Continue to Question 3

3. Prior to the onset of this event, were the MS symptom(s) stable or improving over the last 30 days?

❑ No → IF NO – Continue to Question 4

❑ Yes →

3a. IF YES, was onset within the last 24 hours?
- ❑ Yes IF YES: STOP – Postpone visit for 24 hrs but no more than 7 days

Date rescheduled: __/__/____ (MM DD YYYY)

- ❑ No

IF NO: was onset within the last 7 days?
❑ Yes ❑ No
Continue to Question 4

Page **1** sur **3**

V2.0 2018-10-31

Visit Date : __/__/____ (MM DD YYYY) Patient N°|__|__|__| |__|__|__|

SPI2 Relapse Assessment questionnaire

4. Are the symptom(s) associated with new neurologic findings? ❑ Yes ❑ No

IF YES – In which system(s)?

Pyramidal	❑ Yes	❑ No		Sensory	❑ Yes	❑ No	
Cerebellar	❑ Yes	❑ No		Bowel and/or Bladder	❑ Yes	❑ No	
Brainstem	❑ Yes	❑ No		Mental	❑ Yes	❑ No	
Visual	❑ Yes	❑ No					

If NO to question 2 AND If YES to ANY questions 1, 3, and 4:
Please schedule Relapse Evaluation by blinded rater (Functional Score/EDSS Form)
AND complete questions 5 – 8 of this form

5a. Are the symptom(s) ongoing? ❑ Yes ❑ No ⟶ IF NO, end Date: __/__/____ (MM DD YYYY)

5b. Date of scheduled EDSS: __/__/____ (MM DD YYYY)

6. Please describe event, symptom(s), and treatment(s):_____

_____

_____

_____

7. Was subject treated with steroids? ❑ Yes ❑ No ⟶ IF YES: FILL OUT Concomitant therapy page

The following SPI2 Protocol definitions should be used to answer Q 8, without the new EDSS score:

- **Protocol-defined relapse:**
  - appearance of a new symptom or worsening of an old symptom, attributable to MS
  - symptoms lasting at least 24 hours
  - absence of fever or infection
  - preceded by stability or improvement for at least 30 days
  - subject seen within 7 days of onset
  - change of at least 0.5 on EDSS or 1 pt on 2 FS or 2 pts on 1 FS since the last visit
- **Non Protocol-defined relapse:** same as above but the subject was not seen within 7 days of onset
- **Suspected relapse:** Relapse that fails to meet the above situations, but may has been a relapse – i.e. all circumstances point to relapse, but no change in the EDSS.

Note: **Final determination of relapse status will be made based upon complete data provided to the adjudication committee and not solely the answer to Question 8. Knowledge of associated EDSS score by the blinded rater is not necessary to answer Question 8.**

If Questions 4 – 7 were answered, Question 8 can NOT be answered as "Not a relapse"

8. **According to the above definitions, without the new EDSS score, which is your best estimate of this event as the treating physician (tick only one box)?**

❑ Protocol-Defined Relapse ❑ Non Protocol-Defined Relapse

❑ Suspected Relapse ❑ Not a Relapse

Visit Date : __/__/____ (MM DD YYYY) Patient N°|__|__|__| |__|__|__|

SPI2 Relapse Assessment questionnaire

To correctly assess a relapse, the patient should be assessed during an unscheduled visit (within 7 days of onset if possible) or during the next follow-up visit.

9. Functional score

Date of initial clinical examination: __/__/____ (MM DD YYYY)	Date of follow-up visit: __/__/____ (MM DD YYYY)

Kurtzke Functional Score		Kurtzke Functional Score	
Pyramidal	|___|	Pyramidal	|___|
Cerebellar	|___|	Cerebellar	|___|
Sensory	|___|	Sensory	|___|
Brainstem	|___|	Brainstem	|___|
Visual	|___|	Visual	|___|
Bowel and/or Bladder	|___|	Bowel and/or Bladder	|___|
Mental	|___|	Mental	|___|
Ambulation Score	|___|	**Ambulation Score**	|___|
EDSS	|___|	**EDSS**	|___|

10. Was an MRI performed? ❑ Yes ❑ No
If yes, date: __/__/____ (MM DD YYYY)

11. Is there contrast enhancing lesions? ❑ Yes ❑ No
If yes, please describe lesions: _____

12. New T2 lesions observed? ❑ Yes ❑ No
If yes, please describe lesions: _____

Name: _____

Date: __/__/____ (MM DD YYYY)

Signature:

Annex 4: SPI2 Patient Alert Card

TO HEALTHCARE PROFESSIONALS:

For More Information:
http://medday-lab.com/

Not all clinical laboratory analyzers use the biotin method for testing. Laboratories should be informed that the patient is taking high dose biotin and alternative arrangements must be requested for laboratory tests.

Further information can be obtained by contacting: XX: +XXXXX; US Toll no. +1-978-805-7613 and UK Toll no. +44 1158558 406.

Patient Identification Number

Indication for treatment

Progressive Multiple Sclerosis

Drug dosage

100 mg MD1003 or Placebo.
Take 1 capsule with water 3 times a day just before the morning, noon and evening meals, leaving at least 4 hours between each dose.

Investigator
First name, surname, address, telephone number

medDay PHARMACEUTICALS

SPI2 PATIENT ALERT CARD

You are currently participating in SPI2 study (ClinicalTrials.gov Identifier: NCT02936037):
Effect of MD1003 in Progressive Multiple Sclerosis: A Randomized Double-Blind Placebo Controlled Study

Taking high dose biotin can cause the results of laboratory tests to be inaccurate or misleading.
You must carry this card with you at all times and show it to every healthcare professional you visit so that they may provide you with safe and reliable care.

PM-013-001- MD1003CT2016-01MS-SPI2, MD1003 Patient Alert Card, English, version 1 - 12 Sep 2018

WARNING: TAKING HIGH DOSE BIOTIN CAN CAUSE THE RESULTS OF LABORATORY TESTS TO BE INACCURATE OR MISLEADING

Some laboratory tests use biotin to help measure the results. If you are taking high doses of biotin, the results from such laboratory tests could be falsely high or falsely low. These results would be inaccurate and misleading.

This could lead to you getting a misdiagnosis and can have serious consequences, particularly in an emergency.

This card must be presented to any healthcare professional you visit so that alternative arrangements are requested for laboratory tests.

Biological parameters that can be affected by high dose biotin relate to a broad range of exploratory tests for the following areas:

ANAEMIA
CARDIOLOGY
HORMONES / FERTILITY
THYROID
INFECTIOUS DISEASES
TOXICOLOGY
BONE METABOLISM
ONCOLOGY
SEPSIS / INFLAMMATION

Special attention must be paid to the following biological parameters:

- Cardiac: CPK, BNP, troponin, D-dimer
- Thyroid: TSH, FT3, FT4
- Other: βHCG, PSA, Vitamin D

Your next SPI2 study visit is:

Date: .....

Time: .....

Carry this alert card with you at all times

Show it to every healthcare professional you visit

Return it to your study centre at each visit for a new one

Return your MD1003 bottles dispensed at the last study visit (even if they are empty)

PM-013-001- MD1003CT2016-01MS-SPI2, MD1003 Patient Alert Card, English, version 1 - 12 Sep 2018

Annex 5: Multiple Sclerosis Quality of Life-54 (MSQOL-54)

Multiple Sclerosis Quality of Life

(MSQOL)-54 Instrument

For Further Information, Contact:

Barbara G. Vickrey, MD, MPH
UCLA Department of Neurology
C-128 RNRC; Box 951769
Los Angeles, CA 90095-1769
Voice: 310.206.7671
Fax: 310.794.7716

INSTRUCTIONS:

This survey asks about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3, ...).

If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation in the margin.

Please feel free to ask someone to assist you if you need help reading or marking the form.

1. In general, would you say your health is:
(circle one number)

Excellent……1

Very good……2

Good……3

Fair……4

Poor……5

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

(circle one number)

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

Somewhat better now than one year ago…….2

About the same 3

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

Much worse now than one year ago 5

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

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

13-16. During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

(Circle one number on each line)

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

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

(Circle one number on each line)

	YES	NO
17. Cut down on the amount of time you could spend on work or other activities	1	2
18. Accomplished less than you would like	1	2
19. Didn't do work or other activities as carefully as usual	1	2

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

(circle one number)

Not at all.....1

Slightly 2

Moderately 3

Quite a bit 4

Extremely.....5

Pain

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

(circle one number)

None 1

Very mild..... 2

Mild 3

Moderate..... 4

Severe 5

Very severe..... 6

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

(circle one number)

Not at all..... 1

A little bit 2

Moderately 3

Quite a bit 4

Extremely..... 5

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

How much of the time during the **past 4 weeks**... (Circle one number on each line)

	All of the Time	Most Of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
23. Did you feel full of pep?	1	2	3	4	5	6
24. Have you been a very nervous person?	1	2	3	4	5	6
25. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
26. Have you felt calm and peaceful?	1	2	3	4	5	6
27. Did you have a lot of energy?	1	2	3	4	5	6
28. Have you felt downhearted and blue?	1	2	3	4	5	6
29. Did you feel worn out?	1	2	3	4	5	6
30. Have you been a happy person?	1	2	3	4	5	6
31. Did you feel tired?	1	2	3	4	5	6
32. Did you feel rested on waking in the morning?	1	2	3	4	5	6

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

(circle one number)

All of the time.....1

Most of the time.....2

Some of the time 3

A little of the time.....4

None of the time.....5

Health in General

34-37. How TRUE or FALSE is each of the following statements for you.

(Circle one number on each line)

	Definitely True	Mostly True	Not Sure	Mostly False	Definitely False
34. I seem to get sick a little easier than other people	1	2	3	4	5
35. I am as healthy as anybody I know	1	2	3	4	5
36. I expect my health to get worse	1	2	3	4	5
37. My health is excellent	1	2	3	4	5

Health Distress

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

(Circle one number on each line)

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

Cognitive Function

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

(Circle one number on each line)

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

Sexual Function

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

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

(Circle one number on each line)

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

(Circle one number on each line)

WOMEN	Not a problem	A Little of a Problem	Somewhat of a Problem	Very Much a Problem
46. Lack of sexual interest	1	2	3	4
47. Inadequate lubrication	1	2	3	4
48. Difficulty having orgasm	1	2	3	4
49. Ability to satisfy sexual partner	1	2	3	4

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

(circle one number)

Very satisfied 1

Somewhat satisfied 2

Neither satisfied nor dissatisfied 3

Somewhat dissatisfied 4

Very dissatisfied 5

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

(circle one number)

Not at all 1

Slightly 2

Moderately 3

Quite a bit 4

Extremely 5

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

(circle one number)

Not at all 1

Slightly 2

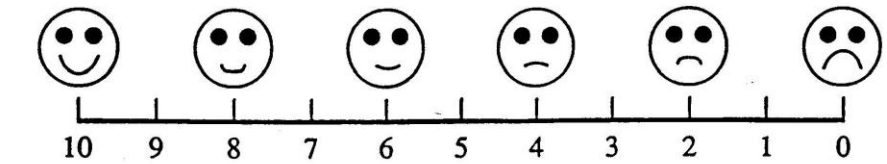
Moderately 3

Quite a bit 4

Extremely 5

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

Circle one number on the scale below:



Best Possible Quality-of-Life

Worst Possible Quality-of-Life

As bad as or worse than being dead

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

(circle one number)

Terrible	1
Unhappy	2
Mostly dissatisfied	3
Mixed - about equally satisfied and dissatisfied	4
Mostly satisfied	5
Pleased	6
Delighted	7

Scoring Forms for Multiple Sclerosis Quality of Life (MSQOL) -54

Table 1
MSQOL-54 Scoring Form

Table 2
MSQOL-54 Physical Health Composite Score

Table 3
MSQOL-54 Mental Health Composite Score

Table 1

MSQOL-54 Scoring Form

Scale/Item Number	Response 1	2	3	4	5	6		Subtotal	Final Score 0-100 point scale
Physical Health									
3.	0	50	100					_____	
4.	0	50	100					_____	
5.	0	50	100					_____	
6.	0	50	100					_____	
7.	0	50	100					_____	
8.	0	50	100					_____	
9.	0	50	100					_____	
10.	0	50	100					_____	
11.	0	50	100					_____	
12.	0	50	100					_____	
							Total:	_____ ÷ 10 =	_____
Role limitations due to physical problems									
13.	0	100						_____	
14.	0	100						_____	
15.	0	100						_____	
16.	0	100						_____	
							Total:	_____ ÷ 4 =	_____
Role limitations due to emotional problems									
17.	0	100						_____	
18.	0	100						_____	
19.	0	100						_____	
							Total:	_____ ÷ 3 =	_____
Pain									
21.	100	80	60	40	20	0		_____	
22.	100	75	50	25	0			_____	
52.	100	75	50	25	0			_____	
							Total:	_____ ÷ 3 =	_____
Emotional well-being									
24.	0	20	40	60	80	100		_____	
25.	0	20	40	60	80	100		_____	
26.	100	80	60	40	20	0		_____	
28.	0	20	40	60	80	100		_____	
30.	100	80	60	40	20	0		_____	
							Total:	_____ ÷ 5 =	_____
Energy									
23.	100	80	60	40	20	0		_____	
27.	100	80	60	40	20	0		_____	
29.	0	20	40	60	80	100		_____	
31.	0	20	40	60	80	100		_____	
32.	100	80	60	40	20	0		_____	
							Total:	_____ ÷ 5 =	_____

Table 1 (cont.) Scale/Item Number	Response 1	2	3	4	5	6	Subtotal	Final Score 0-100 point

Health Perceptions

1.	100	75	50	25	0		_____	
34.	0	25	50	75	100		_____	
35.	100	75	50	25	0		_____	
36.	0	25	50	75	100		_____	
37.	100	75	50	25	0		_____	
						Total:	_____ ÷ 5 =	_____

Social function

20.	100	75	50	25	0		_____	
33.	0	25	50	75	100		_____	
51.	100	75	50	25	0		_____	
						Total:	_____ ÷ 3 =	_____

Cognitive function

42.	0	20	40	60	80	100	_____	
43.	0	20	40	60	80	100	_____	
44.	0	20	40	60	80	100	_____	
45.	0	20	40	60	80	100	_____	
							Total:	_____ ÷ 4 =	_____

Health distress

38.	0	20	40	60	80	100	_____	
39.	0	20	40	60	80	100	_____	
40.	0	20	40	60	80	100	_____	
41.	0	20	40	60	80	100	_____	
							Total:	_____ ÷ 4 =	_____

Sexual function*

46.	100	66.7	33.3	0			_____	
47.	100	66.7	33.3	0			_____	
48.	100	66.7	33.3	0			_____	
49.	100	66.7	33.3	0			_____	
						Total:	_____ ÷ 4 =	_____

Change in health

2.	100	75	50	25	0		_____

Satisfaction with sexual function

50.	100	75	50	25	0		_____

	Response						
Overall quality of life	**1**	**2**	**3**	**4**	**5**	**6**	**7**
53.	(multiply response by 10)						
54.	0	16.7	33.3	50	66.7	83.3	100

Total: _____ ÷ 2 = _____

Note: The total number of items in each scale is listed as the divisor for each subtotal. However, due to missing data, the divisor might actually be less than that if not every item within a given scale has been answered. For example, if item 38 in the Health Distress scale was left blank and the other 3 items in the scale were answered, then the "Total" score for Health Distress would be divided by '3' (instead of '4') to obtain the "Final Score."

* Males and females can be combined in the analysis even though question 47 is different for the two groups. The scale scores can also be reported separately for males and females.

Table 2
Formula for calculating MSQOL-54 Physical Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Physical function	_____	x	.17	=	_____(a)
Health perceptions	_____	x	.17	=	_____(b)
Energy/fatigue	_____	x	.12	=	_____(c)
Role limitations - physical	_____	x	.12	=	_____(d)
Pain	_____	x	.11	=	_____(e)
Sexual function	_____	x	.08	=	_____(f)
Social function	_____	x	.12	=	_____(g)
Health distress	_____	x	.11	=	_____(h)
PHYSICAL HEALTH COMPOSITE: Sum subtotals (a) through (h) =					_____

Table 3
Formula for calculating MSQOL-54 Mental Health Composite Score

MSQOL-54 Scale	Final Scale Score	x	Weight	=	Subtotal
Health distress	_____	x	.14	=	_____(a)
Overall quality of life	_____	x	.18	=	_____(b)
Emotional well-being	_____	x	.29	=	_____(c)
Role limitations - emotional	_____	x	.24	=	_____(d)
Cognitive function	_____	x	.15	=	_____(e)
MENTAL HEALTH COMPOSITE: Sum subtotals (a) through (e) =					_____

Annex 6: Caregiver health-related quality of life in Multiple Sclerosis – CAREQOL-MS

Caregiver health-related quality of life (HRQOL) in Multiple Sclerosis – CAREQOL-MS Questionnaire*
1. I worry about the thoughts regarding multiple sclerosis of the person whom I care for.
2. I reflect about the suffering the limited mobility brings to the person with multiple sclerosis whom I care for.
3. Moving and traveling with the person with multiple sclerosis whom I care for is complicated for me.
4. I worry about the fatigue of the person with multiple sclerosis whom I care for.
5. The fatigue of the person with multiple sclerosis whom I care for poses a greater physical burden to me.
6. The personal hygiene of the person with multiple sclerosis whom I care for proves complicated.
7. I feel alone regarding my tasks of caring for, watching, and supporting a person with multiple sclerosis.
8. I believe that my situation might improve through the collaboration of other caregivers.
9. Caring for a person with multiple sclerosis leaves me with no time for caring for the rest of my family.
10. Multiple sclerosis has affected my social life.
11. Taking care of a person with multiple sclerosis has meant a change in my lifestyle.
12. I miss the company of persons outside the family circle who are acquainted with the disease, so I can share my current situation with them.
13. The attitude of the person with multiple sclerosis whom I care for elicits mood changes in me.
14. The nervousness of the person with multiple sclerosis whom I care for irritates me.
15. I feel sad as a consequence of the multiple sclerosis of the person whom I care for.
16. Multiple sclerosis has affected my relationship with my partner, either regarding our sexual or emotional relationship.
17. I believe that some psychological aid would help me provide better care for the person with multiple sclerosis.
18. I have been suffering from sleep disturbances since I learned that the person whom I care for suffers from multiple sclerosis.
19. The evening care of the person with multiple sclerosis whom I care for prevents me from resting at night.
20. I am scared about the progress and the consequences of multiple sclerosis.
21. My own health has worsened over the course of this year.
22. Ever since the person whom I care for started suffering from multiple sclerosis, I devote less time to my own personal appearance and wellbeing.
23. The care of the person with multiple sclerosis has affected my work life.
24. The multiple sclerosis of the person whom I care for has impacted on my family's financial situation

Annex 7: Columbia-Suicide Severity Rating Scale (C-SSRS)

COLUMBIA-SUICIDE SEVERITY RATING SCALE (C-SSRS)

Since Last Visit

Version 1/14/09

Posner, K.; Brent, D.; Lucas, C.; Gould, M.; Stanley, B.; Brown, G.; Fisher, P.; Zelazny, J.; Burke, A.; Oquendo, M.; Mann, J.

Disclaimer:

This scale is intended to be used by individuals who have received training in its administration. The questions contained in the Columbia-Suicide Severity Rating Scale are suggested probes. Ultimately, the determination of the presence of suicidal ideation or behavior depends on the judgment of the individual administering the scale.

Definitions of behavioral suicidal events in this scale are based on those used in ***The Columbia Suicide History Form****, developed by John Mann, MD and Maria Oquendo, MD, Conte Center for the Neuroscience of Mental Disorders (CCNMD), New York State Psychiatric Institute, 1051 Riverside Drive, New York, NY, 10032. (Oquendo M. A., Halberstam B. & Mann J. J., Risk factors for suicidal behavior: utility and limitations of research instruments. In M.B. First [Ed.]* Standardized Evaluation in Clinical Practice*, pp. 103 -130, 2003.)*

For reprints of the C-SSRS contact Kelly Posner, Ph.D., New York State Psychiatric Institute, 1051 Riverside Drive, New York, New York, 10032; inquiries and training requirements contact posnerk@nyspi.columbia.edu

C-SSRS Since Last Visit - United States/English - Mapi.
C-SSRS-SinceLastVisit_AU5.1_eng-USori.doc

SUICIDAL IDEATION

Ask questions 1 and 2. If both are negative, proceed to "Suicidal Behavior" section. If the answer to question 2 is "yes", ask questions 3, 4 and 5. If the answer to question 1 and/or 2 is "yes", complete "Intensity of Ideation" section below.	**Since Last Visit**
1. Wish to be Dead Subject endorses thoughts about a wish to be dead or not alive anymore, or wish to fall asleep and not wake up. ***Have you wished you were dead or wished you could go to sleep and not wake up?*** If yes, describe:	Yes ☐ No ☐
2. Non-Specific Active Suicidal Thoughts General non-specific thoughts of wanting to end one's life/commit suicide (e.g., *"I've thought about killing myself"*) without thoughts of ways to kill oneself/associated methods, intent, or plan during the assessment period. ***Have you actually had any thoughts of killing yourself?*** If yes, describe:	Yes ☐ No ☐
3. Active Suicidal Ideation with Any Methods (Not Plan) without Intent to Act Subject endorses thoughts of suicide and has thought of at least one method during the assessment period. This is different than a specific plan with time, place or method details worked out (e.g., thought of method to kill self but not a specific plan). Includes person who would say, *"I thought about taking an overdose but I never made a specific plan as to when, where or how I would actually do it.....and I would never go through with it".* ***Have you been thinking about how you might do this?*** If yes, describe:	Yes ☐ No ☐
4. Active Suicidal Ideation with Some Intent to Act, without Specific Plan Active suicidal thoughts of killing oneself and subject reports having some intent to act on such thoughts, as opposed to *"I have the thoughts but I definitely will not do anything about them".* ***Have you had these thoughts and had some intention of acting on them?*** If yes, describe:	Yes ☐ No ☐
5. Active Suicidal Ideation with Specific Plan and Intent Thoughts of killing oneself with details of plan fully or partially worked out and subject has some intent to carry it out. ***Have you started to work out or worked out the details of how to kill yourself? Do you intend to carry out this plan?*** If yes, describe:	Yes ☐ No ☐

INTENSITY OF IDEATION

The following features should be rated with respect to the most severe type of ideation (i.e.,1-5 from above, with 1 being the least severe and 5 being the most severe). ***Most Severe Ideation:*** _____ _____ ***Type # (1-5)*** ***Description of Ideation***	Most Severe
Frequency ***How many times have you had these thoughts?*** (1) Less than once a week (2) Once a week (3) 2-5 times in week (4) Daily or almost daily (5) Many times each day	____
Duration ***When you have the thoughts how long do they last?*** (1) Fleeting - few seconds or minutes (2) Less than 1 hour/some of the time (3) 1-4 hours/a lot of time (4) 4-8 hours/most of day (5) More than 8 hours/persistent or continuous	____
Controllability ***Could/can you stop thinking about killing yourself or wanting to die if you want to?*** (1) Easily able to control thoughts (2) Can control thoughts with little difficulty (3) Can control thoughts with some difficulty (4) Can control thoughts with a lot of difficulty (5) Unable to control thoughts (0) Does not attempt to control thoughts	____
Deterrents ***Are there things - anyone or anything (e.g., family, religion, pain of death) - that stopped you from wanting to die or acting on thoughts of committing suicide?*** (1) Deterrents definitely stopped you from attempting suicide (2) Deterrents probably stopped you (3) Uncertain that deterrents stopped you (4) Deterrents most likely did not stop you (5) Deterrents definitely did not stop you (0) Does not apply	____
Reasons for Ideation ***What sort of reasons did you have for thinking about wanting to die or killing yourself? Was it to end the pain or stop the way you were feeling (in other words you couldn't go on living with this pain or how you were feeling) or was it to get attention, revenge or a reaction from others? Or both?*** (1) Completely to get attention, revenge or a reaction from others (2) Mostly to get attention, revenge or a reaction from others (3) Equally to get attention, revenge or a reaction from others and to end/stop the pain (4) Mostly to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (5) Completely to end or stop the pain (you couldn't go on living with the pain or how you were feeling) (0) Does not apply	____

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SUICIDAL BEHAVIOR *(Check all that apply, so long as these are separate events; must ask about all types)*	**Since Last Visit**
Actual Attempt: A potentially self-injurious act committed with at least some wish to die, *as a result of act*. Behavior was in part thought of as method to kill oneself. Intent does not have to be 100%. If there is ***any*** intent/desire to die associated with the act, then it can be considered an actual suicide attempt. ***There does not have to be any injury or harm***, just the potential for injury or harm. If person pulls trigger while gun is in mouth but gun is broken so no injury results, this is considered an attempt. Inferring Intent: Even if an individual denies intent/wish to die, it may be inferred clinically from the behavior or circumstances. For example, a highly lethal act that is clearly not an accident so no other intent but suicide can be inferred (e.g., gunshot to head, jumping from window of a high floor/story). Also, if someone denies intent to die, but they thought that what they did could be lethal, intent may be inferred. ***Have you made a suicide attempt?*** ***Have you done anything to harm yourself?*** ***Have you done anything dangerous where you could have died?*** ***What did you do?*** ***Did you_____as a way to end your life?*** ***Did you want to die (even a little) when you_____?*** ***Were you trying to end your life when you_____?*** ***Or Did you think it was possible you could have died from_____?*** ***Or did you do it purely for other reasons / without ANY intention of killing yourself (like to relieve stress, feel better, get sympathy, or get something else to happen)?*** (Self-Injurious Behavior without suicidal intent) If yes, describe: **Has subject engaged in Non-Suicidal Self-Injurious Behavior?**	Yes ☐ No ☐ Total # of Attempts _____ Yes ☐ No ☐
Interrupted Attempt: When the person is interrupted (by an outside circumstance) from starting the potentially self-injurious act *(if not for that, actual attempt would have occurred)*. Overdose: Person has pills in hand but is stopped from ingesting. Once they ingest any pills, this becomes an attempt rather than an interrupted attempt. Shooting: Person has gun pointed toward self, gun is taken away by someone else, or is somehow prevented from pulling trigger. Once they pull the trigger, even if the gun fails to fire, it is an attempt. Jumping: Person is poised to jump, is grabbed and taken down from ledge. Hanging: Person has noose around neck but has not yet started to hang - is stopped from doing so. ***Has there been a time when you started to do something to end your life but someone or something stopped you before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of interrupted _____
Aborted Attempt: When person begins to take steps toward making a suicide attempt, but stops themselves before they actually have engaged in any self-destructive behavior. Examples are similar to interrupted attempts, except that the individual stops him/herself, instead of being stopped by something else. ***Has there been a time when you started to do something to try to end your life but you stopped yourself before you actually did anything?*** If yes, describe:	Yes ☐ No ☐ Total # of aborted _____
Preparatory Acts or Behavior: Acts or preparation towards imminently making a suicide attempt. This can include anything beyond a verbalization or thought, such as assembling a specific method (e.g., buying pills, purchasing a gun) or preparing for one's death by suicide (e.g., giving things away, writing a suicide note). ***Have you taken any steps towards making a suicide attempt or preparing to kill yourself (such as collecting pills, getting a gun, giving valuables away or writing a suicide note)?*** If yes, describe:	Yes ☐ No ☐
Suicidal Behavior: Suicidal behavior was present during the assessment period?	Yes ☐ No ☐
Suicide:	Yes ☐ No ☐
Answer for Actual Attempts Only	Most Lethal Attempt Date:
Actual Lethality/Medical Damage: 0. No physical damage or very minor physical damage (e.g., surface scratches). 1. Minor physical damage (e.g., lethargic speech; first-degree burns; mild bleeding; sprains). 2. Moderate physical damage; medical attention needed (e.g., conscious but sleepy, somewhat responsive; second-degree burns; bleeding of major vessel). 3. Moderately severe physical damage; *medical* hospitalization and likely intensive care required (e.g., comatose with reflexes intact; third-degree burns less than 20% of body; extensive blood loss but can recover; major fractures). 4. Severe physical damage; *medical* hospitalization with intensive care required (e.g., comatose without reflexes; third-degree burns over 20% of body; extensive blood loss with unstable vital signs; major damage to a vital area). 5. Death	*Enter Code* _____
Potential Lethality: Only Answer if Actual Lethality=0 Likely lethality of actual attempt if no medical damage (the following examples, while having no actual medical damage, had potential for very serious lethality: put gun in mouth and pulled the trigger but gun fails to fire so no medical damage; laying on train tracks with oncoming train but pulled away before run over). 0 = Behavior not likely to result in injury 1 = Behavior likely to result in injury but not likely to cause death 2 = Behavior likely to result in death despite available medical care	*Enter Code* _____

Annex 8: World Medical Association Declaration of Helsinki (2013 version)

WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects (2013 version)

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964

and amended by the:

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

53rd WMA General Assembly, Washington DC, USA, October 2002 (Note of Clarification added)

55th WMA General Assembly, Tokyo, Japan, October 2004 (Note of Clarification added)

59th WMA General Assembly, Seoul, Republic of Korea, October 2008

64th WMA General Assembly, Fortaleza, Brazil, October 2013

Preamble

1. The World Medical Association (WMA) has developed the Declaration of Helsinki as a statement of ethical principles for medical research involving human subjects, including research on identifiable human material and data.

The Declaration is intended to be read as a whole and each of its constituent paragraphs should be applied with consideration of all other relevant paragraphs.

2. Consistent with the mandate of the WMA, the Declaration is addressed primarily to physicians. The WMA encourages others who are involved in medical research involving human subjects to adopt these principles.

General Principles

3. The Declaration of Geneva of the WMA binds the physician with the words, “The health of my patient will be my first consideration,” and the International Code of Medical Ethics declares that, “A physician shall act in the patient's best interest when providing medical care.”

4. It is the duty of the physician to promote and safeguard the health, well-being and rights of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

5. Medical progress is based on research that ultimately must include studies involving human subjects.

6. The primary purpose of medical research involving human subjects is to understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). Even the best proven interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality.

7. Medical research is subject to ethical standards that promote and ensure respect for all human subjects and protect their health and rights.

8. While the primary purpose of medical research is to generate new knowledge, this goal can never take precedence over the rights and interests of individual research subjects.

9. It is the duty of physicians who are involved in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects. The responsibility for the protection of research subjects must always rest with the physician or other health care professionals and never with the research subjects, even though they have given consent.

10. Physicians must consider the ethical, legal and regulatory norms and standards for research involving human subjects in their own countries as well as applicable international norms and standards. No national or international ethical, legal or regulatory requirement should reduce or eliminate any of the protections for research subjects set forth in this Declaration.

11. Medical research should be conducted in a manner that minimises possible harm to the environment.

12. Medical research involving human subjects must be conducted only by individuals with the appropriate ethics and scientific education, training and qualifications. Research on patients or healthy volunteers requires the supervision of a competent and appropriately qualified physician or other health care professional.

13. Groups that are underrepresented in medical research should be provided appropriate access to participation in research.

14. Physicians who combine medical research with medical care should involve their patients in research only to the extent that this is justified by its potential preventive, diagnostic or therapeutic value and if the physician has good reason to believe that participation in the research study will not adversely affect the health of the patients who serve as research subjects.

15. Appropriate compensation and treatment for subjects who are harmed as a result of participating in research must be ensured.

Risks, Burdens and Benefits

16. In medical practice and in medical research, most interventions involve risks and burdens.

Medical research involving human subjects may only be conducted if the importance of the objective outweighs the risks and burdens to the research subjects.

17. All medical research involving human subjects must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation.

Measures to minimise the risks must be implemented. The risks must be continuously monitored, assessed and documented by the researcher.

18. Physicians may not be involved in a research study involving human subjects unless they are confident that the risks have been adequately assessed and can be satisfactorily managed.

When the risks are found to outweigh the potential benefits or when there is conclusive proof of definitive outcomes, physicians must assess whether to continue, modify or immediately stop the study.

Vulnerable Groups and Individuals

19. Some groups and individuals are particularly vulnerable and may have an increased likelihood of being wronged or of incurring additional harm.

All vulnerable groups and individuals should receive specifically considered protection.

20. Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group and the research cannot be carried out in a non-vulnerable group.

In addition, this group should stand to benefit from the knowledge, practices or interventions that result from the research.

Scientific Requirements and Research Protocols

21. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and adequate laboratory and, as appropriate, animal experimentation. The welfare of animals used for research must be respected.

22. The design and performance of each research study involving human subjects must be clearly described and justified in a research protocol.

The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study.

In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.

Research Ethics Committees

23. The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must be transparent in its functioning, must be independent of the researcher, the sponsor and any other undue influence and must be duly qualified. It must take into consideration the laws and regulations of the country or countries in which the research is to be performed as well as applicable international norms and standards but these must not be allowed to reduce or eliminate any of the protections for research subjects set forth in this Declaration.

The committee must have the right to monitor ongoing studies. The researcher must provide monitoring information to the committee, especially information about any serious adverse events. No amendment to the protocol may be made without consideration and approval by the committee. After the end of the study, the researchers must submit a final report to the committee containing a summary of the study's findings and conclusions.

Privacy and Confidentiality

24. Every precaution must be taken to protect the privacy of research subjects and the confidentiality of their personal information.

Informed Consent

25. Participation by individuals capable of giving informed consent as subjects in medical research must be voluntary. Although it may be appropriate to consult family members or community leaders, no individual capable of giving informed consent may be enrolled in a research study unless he or she freely agrees.

26. In medical research involving human subjects capable of giving informed consent, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal. Special attention should be given to the specific information needs of individual potential subjects as well as to the methods used to deliver the information.

After ensuring that the potential subject has understood the information, the physician or another appropriately qualified individual must then seek the potential subject's freely-given informed consent,

preferably in writing. If the consent cannot be expressed in writing, the non-written consent must be formally documented and witnessed.

All medical research subjects should be given the option of being informed about the general outcome and results of the study.

27. When seeking informed consent for participation in a research study the physician must be particularly cautious if the potential subject is in a dependent relationship with the physician or may consent under duress. In such situations the informed consent must be sought by an appropriately qualified individual who is completely independent of this relationship.

28. For a potential research subject who is incapable of giving informed consent, the physician must seek informed consent from the legally authorised representative. These individuals must not be included in a research study that has no likelihood of benefit for them unless it is intended to promote the health of the group represented by the potential subject, the research cannot instead be performed with persons capable of providing informed consent, and the research entails only minimal risk and minimal burden.

29. When a potential research subject who is deemed incapable of giving informed consent is able to give assent to decisions about participation in research, the physician must seek that assent in addition to the consent of the legally authorised representative. The potential subject's dissent should be respected.

30. Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents giving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative.

31. The physician must fully inform the patient which aspects of their care are related to the research. The refusal of a patient to participate in a study or the patient's decision to withdraw from the study must never adversely affect the patient-physician relationship.

32. For medical research using identifiable human material or data, such as research on material or data contained in biobanks or similar repositories, physicians must seek informed consent for its collection, storage and/or reuse. There may be exceptional situations where consent would be impossible or impracticable to obtain for such research. In such situations the research may be done only after consideration and approval of a research ethics committee.

Use of Placebo

33. The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:

Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or

Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention

and the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.

Extreme care must be taken to avoid abuse of this option.

Post-Trial Provisions

34. In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process.

Research Registration and Publication and Dissemination of Results

35. Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject.

36. Researchers, authors, sponsors, editors and publishers all have ethical obligations with regard to the publication and dissemination of the results of research. Researchers have a duty to make publicly available the results of their research on human subjects and are accountable for the completeness and accuracy of their reports. All parties should adhere to accepted guidelines for ethical reporting. Negative and inconclusive as well as positive results must be published or otherwise made publicly available. Sources of funding, institutional affiliations and conflicts of interest must be declared in the publication. Reports of research not in accordance with the principles of this Declaration should not be accepted for publication.

Unproven Interventions in Clinical Practice

37. In the treatment of an individual patient, where proven interventions do not exist or other known interventions have been ineffective, the physician, after seeking expert advice, with informed consent from the patient or a legally authorised representative, may use an unproven intervention if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. This intervention should subsequently be made the object of research, designed to evaluate its safety and efficacy. In all cases, new information must be recorded and, where appropriate, made publicly available.