SERENDEM study: MD1003 in patients suffering from demyelinating neuropathies, an open label pilot study

CLINICAL TRIAL PROTOCOL

Version No: 4 Dated: 10-Feb-2017

Short title: SERENDEM

Protocol No: MD1003CT2015-01 SERENDEM

EudraCT No: 2015-001150-15

SPONSOR: MEDDAY SA

Address: 96 Boulevard Haussmann
75008 Paris France

SIGNATURE PAGE

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.

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

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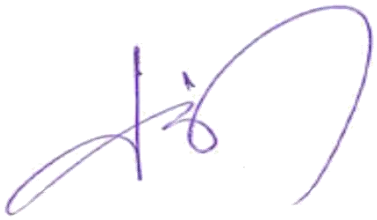


Table of content

1 ABREVIATIONS

AE Adverse event
ALT Alanine aminotransferase
APTT Activated partial thromboplastin time
AST Aspartate aminotransferase
CRF Case report form
CSF Cerebrospinal fluid
DNA Deoxyribonucleic Acid
DSMB Data safety monitoring board
CRF electronic case report form
EKG / ECG Electrocardiogram
FAS Full analysis data set
FDA Food and Drug Administration
GCP Good clinical practice
GGT Gamma glutamyl transferase
IMP Investigational Medicinal Product
INR International normalized ratio
IRB / IEC Institutional Review Board / Independent Ethics Committee
MS Multiple sclerosis
NCV Nervous conduction velocity
NIMP Non investigational medicinal product
PC Personal computer
PP Per protocol
PT Prothrombin time
QoL Quality of life
RBC Red blood cell
SAE Serious adverse event
SAP Statistical analyses plan
SD Standard deviation
SUSAR Suspected unexpected serious adverse reaction
WBC White blood cell

2 STUDY SUMMARY

Study Protocol Title	SERENDEM study: MD1003 in patients suffering from demyelinating neuropathies, an open label pilot study
Short title	SERENDEM
Study Protocol Number	MD1003CT2015-01-SERENDEM
EudraCT Number	2015-001150-15
Methodology and study design	open label, uncontrolled, pilot study in 3 distinct groups of 5 patients suffering from a specific aetiology pattern of peripheral neuropathy
Study Center	Henri Mondor Hospital, Créteil France
Objectives	To assess efficacy of MD1003 given orally thrice a day on motor and sensory conduction, in patients suffering from demyelinating polyneuropathies.
Number of patients	15 patients: 3 groups of 5 patients (CIDP, anti-MAG, CMT1a, CMT1b)

Diagnosis and main inclusion criteria	• Male and female aged between 20 and 85 years.
	• Patients fulfilling one of the following diagnosis on both clinical and neurophysiological grounds, either with:
	  • CIDP
	  • proven genetic diagnosis of CMT1a
	  • proven genetic diagnosis of CMT1b
	  • anti-MAG polyneuropathy
	• Electrophysiological parameters worsening for the past 3 years
	• Available EMG record, performed during the past 6 months to assess variability of NCV parameters
	• Having given informed consent

Non-inclusion criteria	• For CIDP patients, relapse in the past 3 months before inclusion • Pregnancy • Women of childbearing potential without effective contraception
Investigational Product	MD1003, 100 mg capsule
Control therapy	No control arm
Concomitant therapies	Best standard of care
Duration of administration	48 weeks
Evaluation criteria	Primary objective:

	The primary endpoint will be evaluated as follows: significant change from baseline to week 48 in at least two out of the four criteria of demyelination: • motor nerve conduction velocity, • distal latency, • F wave latency, • length of motor nerve potential, 8 nerves will be assessed for those 4 parameters. Change will be considered significant when the last value is 10% improved compared to the baseline value for 2 out of the 4 parameters in at least 3 nerves out of 8 investigated nerves. The secondary endpoints are changes from baseline to week 48 in ONLS, MRC, INCAT, Posturometry, Timed 10-meter walk test, 6-min walk test, Min-max absolute refractory period, Refractoriness, Supernormality, Strength-duration time constant, Rheobase Secondary objective: To evaluate the safety of high doses of biotin.
Statistical methodology	Exploratory descriptive analyses
Duration of patient participation	48 weeks
Study duration	52 weeks

3 STUDY RATIONALE – HISTORICAL BACKGROUND

3.1 Disease aetiology, pathology, symptomatology and current treatments

3.1.1 Aetiology

3.1.1.1 Chronic inflammatory demyelinating polyradiculoneuropathy

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an acquired paralytic illness affecting peripheral nerves and caused by a demyelinating process.

CIDP is a rare disease. The various epidemiological studies show that prevalence may vary from 1.24/100 000 (Laughlin 2009) to 8.9/100 000 (Mahdi-Rogers 2013). Due to the ambiguities of diagnosing CIDP, the true prevalence of the disease may be underestimated or overestimated. The etiology of CIDP is unknown even if rare cases can be associated with different conditions, such as diabetes mellitus, sarcoidosis, disseminated lupus erythematosus, or idiopathic monoclonal gammopathy.

3.1.1.2 Demyelinating neuropathy associated with immunoglobulin M (IgM) monoclonal gammopathy and antibodies against myelin-associated glycoprotein (MAG)

Polyneuropathy associated with IgM monoclonal gammopathy and antibodies against myelin-associated glycoprotein (MAG) belongs to the group of chronic demyelinating polyneuropathies. It is a chronic progressive disorder that leads to a variable degree of functional impairment and disability.

3.1.1.3 Charcot Marie Tooth Ia and Ib (CMT Ia and Ib) neuropathy

Charcot-Marie-Tooth disease Type 1A (CMT1a) belongs to the group of inherited, progressive, chronic sensory and motor peripheral neuropathies referred to as Charcot-Marie-Tooth (CMT) disease or as “Hereditary Motor and Sensory Neuropathy” (HMSN). CMT1a accounts for 70% of patients with CMT, with an estimated prevalence of 10 in 100,000. CMT1a is an autosomal dominant disorder caused in the vast majority of cases by a 1.4 megabase-long duplication of chromosome 17p11.2, encompassing the PMP22 gene.

Charcot-Marie-Tooth disease Type 1B (CMT1b) belongs to the group of inherited, progressive, chronic sensory and motor peripheral neuropathies referred to as Charcot-Marie-Tooth (CMT) disease or as “Hereditary Motor and Sensory Neuropathy” (HMSN). CMT1b accounts for 6%-10% of patients with CMT, with an estimated prevalence of 1.5:100.000. CMT1b is an autosomal dominant disorder caused in the vast majority of cases by mutations change in the single protein building blocks (amino acids) in myelin protein zero (MPZ), located in the chromosome 1.

3.1.2 Clinical symptoms and evolution

3.1.2.1 Chronic inflammatory demyelinating polyneuropathy

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune neuropathy; its diagnosis has challenged physicians since its first description by Dyck and others (Dyck, 1975). As a result, this condition has undergone more than 10 revisions of its diagnostic criteria (Dyck, 1975; Hughes *et al.*, 2001; 2005; Barohn *et al.*, 1989; Nevo and Topaloglu, 2002; Saperstein *et al.*, 2001; Thaisetthawatkul *et al.*, 2002; Magda *et al.*, 2003; AAN task Force, 1991; Joint Task Force of the EFNS and the PNS, 2010). These criteria are based mainly on clinical and neurophysiological parameters that may help distinguish CIDP from other neuropathies, including chronic idiopathic axonal polyneuropathy, diabetic polyneuropathies and amyotrophic lateral sclerosis. Furthermore, several variants of inflammatory neuropathy have been defined, including multifocal motor neuropathy with conduction blocks, multifocal motor and sensory neuropathy with conduction blocks and distal acquired demyelinating polyneuropathy (Larue *et al.*, 2011; Viala *et al.*, 2010).

The most recent recommendation by the European Federation of Neurological Societies allows for the distinction among definite, probable and possible CIDP diagnoses based on the clinical diagnostic criteria of typical CIDP and atypical CIDP (Joint Task Force of the European Federation of the Neurological Societies [EFNS] and the Peripheral Nerve Society [PNS], 2010. The clinical diagnosis of typical CIDP is easier to identify than the diagnosis of atypical CIDP due to the possibility of variants with pure motor or pure sensory presentations and asymmetric or focal presentations with atypical CIDP. Moreover, the existence of several neurophysiological classifications of demyelination and the possibility of presentations with axonal features exacerbates the process of accurate classification.

Typical CIDP is characterized by a chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and absent or reduced tendon reflexes in all extremities.

Atypical CIDP (still considered CIDP but with different features) may have normal tendon reflexes in unaffected limbs: predominantly distal (distal acquired demyelinating symmetric, DADS) or asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb) ; or pure motor ; or pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron) neurological deficits.

The temporal course may be characterized by a subacute onset or acute onset, a relapsing-remitting course or a progressive course (Joint Task Force of the EFNS and the PNS, 2010). The long term prognosis of CIDP patients is not so good after five years with 39% of patients still requiring immune treatments and 13% with severe disabilities (Kuwabara 2006). The prognosis of CIDP is related to axonal loss secondary to inflammatory demyelination (Hughes et al., 2006; van Schaik et al., 2006).

3.1.2.2 Demyelinating neuropathy associated with immunoglobulin M (IgM) monoclonal gammopathy and antibodies against myelin-associated glycoprotein (MAG)

Polyneuropathy associated with IgM monoclonal gammopathy and antibodies against myelin-associated glycoprotein (MAG) is a chronic progressive disorder that leads to a variable degree of functional impairment and disability. Most patients have a symmetric sensorimotor polyneuropathy, sensory ataxia, painful paresthesia and upper limb tremor. The disease may progress slowly over many years in some patients, whereas others develop significant disability mostly due to dysesthesia and ataxia; thus, there is a need to develop effective treatments (EFNS and PNS guideline, 2010).

3.1.2.3 Charcot Marie Tooth Ia and Ib (CMT Ia and Ib) neuropathy

Typical clinical features of CMT1A and CMT1B are similar including weakness of the foot and lower leg and foot deformities (most frequently pes cavus), which appear to be due to weakness of the small intrinsic muscles of the feet. Later in the disease, weakness and muscle atrophy may occur in the hands, resulting in difficulty with fine motor skills. The severity of symptoms is quite variable from one patient to another and even among affected members of the same family.

3.1.3 Pathophysiology

3.1.3.1 Chronic inflammatory demyelinating polyneuropathy

The underlying pathologic mechanisms are still unclear but an autoimmune aetiology is probable. Various mechanisms may be instrumental in CIDP including presence of auto-antibodies, inflammatory mediators (tumor necrosis factor alpha, interleukin 1, matrix metalloproteinases 2 and 9, complement fractions, chemokines), lymphocyte proliferation, modulation of the Fcγ RII / Fcγ RIII ratio on macrophages. Whatever the involved mechanisms, the consequences include alteration of nerve excitability due to demyelination, decrease of Na+/K+ ATPase pump function, intra-axonal Na+ accumulation associated with energetic failure, leading process to axonal degeneration in inflammatory demyelinating processes (Stys and Waxman, 1994; Bechtold and Smith, 2005).

3.1.3.2 Demyelinating neuropathy associated with immunoglobulin M (IgM) monoclonal gammopathy and antibodies against myelin-associated glycoprotein (MAG)

A causative role of the IgM M protein in the polyneuropathy is illustrated by the presence of circulating anti MAG antibodies or other antibodies directed at the myelin sheath of peripheral nerves that lead to enlargement of the myelin sheath. Patients present with a striking immunochemical profile, suggesting the possibility of an autoimmune mechanism: monoclonal IgM recognizes a carbohydrate MAG epitope, which is shared with a number of other glycoconjugates involved in cell adhesion, including the Po glycoprotein of myelin, peripheral myelin protein–22, sulfated sphingolipid, and other related glycolipids (Latov et al. , 1995; Eurelings et al., 2001). The nerve examination shows widening of myelin lamellae.

3.1.3.3 Charcot Marie Tooth Ia and Ib (CMT Ia and Ib) neuropathy

PMP22 encodes a transmembrane peripheral myelin protein. The duplication of the PMP22 gene results in its overexpression and in abnormal Schwann cell differentiation. The consequences are a homogeneous and diffuse nerve conduction slowing and dysmyelination, eventually leading to axonal loss and muscle wasting.

The altered myelin protein zero probably cannot interact properly with other myelin components, which may disrupt the formation and maintenance of myelin. As a result, peripheral nerve cells cannot activate muscles used for movement or relay information from sensory cells back to the brain, leading to the weakness and sensory problems characteristic of Charcot-Marie-Tooth disease.

3.1.4 Current treatments

3.1.4.1 Chronic inflammatory demyelinating polyneuropathy

Corticosteroids, plasma exchange, and intravenous (IV) immunoglobulin (IVIg) have shown efficacy in controlled trials. The choice of therapy depends on several factors, including disease severity, concomitant illnesses, adverse-effect profile, potential drug interactions, venous access, age-related risks, and cost of treatment. Corticosteroids is considered as a first line or second line treatment option and have been used to treat CIDP for a long time. It is usually initiated with a dose of 1mg/kg with a tapering after several months according to clinical response. IVIg is widely used in the treatment of CIDP. Treatment by intravenous immunoglobulins, (IVIgs) can provide significant clinical benefits in more than 60% of CIDP patients (Vermeulen et al., 1993; Hahn et al., 1996; Mendell et al., 2001). Clinical improvement often occurs within a few days following IVIg infusions (Kaji et al., 1992; Chaudhry et al., 1993; Nobile-Orazio et al., 1993; Van den Berg et al., 1995; 1998; Léger et al., 2001). However, such improvement usually lasts for a few weeks and periodic IVIg infusions are required to maintain therapeutic benefit. Finally, the long term effect of IVIG has not been investigated for more than 6 months (Hughes 2009). Moreover, there is no data on the prevention of axonal degeneration with these treatment options.

3.1.4.2 Demyelinating neuropathy associated with immunoglobulin M (IgM) monoclonal gammopathy and antibodies against myelin-associated glycoprotein (MAG)

There is no consensus about the best treatment strategy, besides the timing of initiation of treatment has not been determined for anti-MAG neuropathy. Immunotherapy and chemotherapy may act through direct suppression or elimination of the B cell clone, or by suppression of the inflammatory cascade (Lunn et Al. 2012). There is insufficient evidence from most pilot studies or randomized controlled trials (RCT) on IgM anti-MAG demyelinating neuropathy to recommend any particular immunotherapy. The last controlled trial for rituximab did not show any benefit (Léger et Al. 2013).

3.1.4.3 Charcot Marie Tooth Ia and Ib (CMT Ia and Ib) neuropathy

There is currently no approved treatment for CMT1A and for CMT1B. Supportive therapies mainly address disease symptoms such as neuropathic pain, weakness and limb deformities. They include

treatment of pain (anti-inflammatory/analgesics, anti-depressants or anti-convulsants for neuropathic pain), physiotherapy (muscle strength training), occupational therapy, orthopaedic devices (including braces and high top shoes) and orthopaedic surgery. However, these treatments are not sufficient to limit impairment of motor function and worsening of disability. Ascorbic acid (AA) has shown to promote myelination in vitro and to possibly decrease PMP22 expression. Following this, six clinical trials assessing efficacy and tolerability of 1- or 2-year AA treatment were published, but no clinical benefit was observed in any of these trials. In addition, the results from a double-blind, randomized, placebo-controlled dose ranging phase 2 study of PXT3003 (a low dose combination of three already approved compounds: (RS)-baclofen, naltrexone hydrochloride and D-sorbitol) were recently published. This trial confirmed the potential good safety and tolerability of PXT3003. The highest dose showed preliminary but consistent evidence of efficacy, with a modest clinical benefit in these adult patients.

3.2 Summary of findings from nonclinical and clinical studies with biotin

3.2.1 Roles of biotin in normal cell metabolism

Biotin (or vitamin H) is a ubiquitous water-soluble vitamin which is naturally found in many foods, such as offal, eggs and some vegetables. In mammals, biotin acts as a coenzyme for four important carboxylases involved in key steps of energy metabolism and fatty acids synthesis. Biotin-dependent mitochondrial carboxylases include PC (pyruvate carboxylase), PCC (propionyl CoA carboxylase), and MCC (methylcrotonyl CoA carboxylase). All these three enzymes ultimately provide intermediates for the Krebs cycle including acetyl CoA, succinyl-CoA and oxaloacetate. These anaplerotic reactions trigger increased ATP production in neurons (Rinholm et al., 2011).

3.2.2 Biotin and biotin-responsive basal ganglia disease "BBGD".

High doses of biotin have been demonstrated to be a therapeutic option in "biotin responsive basal ganglia disease", an orphan neurometabolic disease (Ozand et al., 1998; Debs et al., 2010) which is caused by mutations in the SLC19A3 gene coding for a thiamine transporter (Zeng et al., 2005; Subramanian et al., 2006). A hypothesis explaining the effect of high doses of biotin in BBGD is that biotin activates the Krebs cycle downstream of the pyruvate and α-ketoglutarate dehydrogenases that are impaired in situations of defect in thiamine transport.

3.2.3 Biotin and primary or secondary progressive multiple sclerosis

Previous human experience in a pilot study and results of two phase IIb/III studies (EudraCT No. 2013-002113-35 and 2013-002112-27, namely MS-SPI study and MS-ON study, respectively) have provided evidences of a favourable benefit/risk balance of MD1003 (biotin 300 mg/day) in adult patients with progressive MS, but not in MS patients with relapsing-remitting MS.

The randomized, double-blinded MS-SPI study included adult patients with PP and SP MS with no evidence of inflammatory activity (n=103 in the MD1003 group and n=54 in the placebo group). Improvement was defined as either a decrease in disability score (EDSS) or an improvement in TW25 (a timed 25-foot walk) as compared to the best EDSS and TW25 scores obtained either at the screening or randomisation visits. Results demonstrated a strong and clinically meaningful benefit of MD1003 compared to placebo with (1) improvement of a significant proportion of patients after 9 months confirmed at 12 months (primary endpoint, p=0.005), (2) stabilized mean EDSS score (p=0.014) and (3) better clinical global impression of change (p<0.0001).

The randomized, double-blinded MS-ON study included adult patients with either visual loss following an optic neuritis relapse (ON relapses, n=62) or chronic progressive optic neuritis (progressive ON, n=31). The primary endpoint was the mean change in 100% contrast visual acuity (VA) at 6 months from baseline of the worst eye. In patients with ON relapses, VA improved in both placebo and MD1003 groups by a mean of 0.06 LogMAR, i.e. 3 letters in both groups, without any superiority of MD1003. In the progressive ON subgroup, VA worsened by a mean of 0.03 LogMAR in the placebo group, while it improved by a mean of 0.06 LogMAR in the MD1003 group. Although the number of patients was too

small to reach statistical significance, these results are in line with the positive results of the MS-SPI trial and indicate that MD1003 should be indicated in progressive MS only.

It is hypothesized that the positive effects of high doses of biotin in progressive MS are linked to:

(1) Increased energy production in demyelinated neurons. This would avoid neurodegeneration and would improve neuronal functioning.

(2) Stimulation of myelin repair through activation of the acetyl CoA carboxylase in oligodendrocytes. This induction of myelin repair could explain the very long-term effects of the treatment with continuous improvement overtime even after 14 months of treatment.

We hypothesized that chronic inflammatory demyelinating polyradiculoneuropathy, demyelinating neuropathy associated with immunoglobulin M (IgM) monoclonal gammopathy and antibodies against myelin-associated glycoprotein (MAG), Charcot Marie Tooth Ia and Ib (CMT Ia and Ib) neuropathy and progressive multiple sclerosis share some similarities including demyelinating processes, and chronic progressive disorders leading to a variable degree of functional impairment and disability.

Considering previous positive results in progressive MS it is justified to investigate the MD1003 in a population of demyelinating neuropathies of different aetiologies, as a proof of concept / pilot study using various measurement methods.

4 STUDY OBJECTIVES

The primary objective of the study is to assess the effect of MD1003 on motor and sensory conduction, in patients suffering from demyelinating polyneuropathies.

The secondary objective is to evaluate safety of MD1003 in this patient population.

This pilot study will not be controlled by a placebo. It is aiming to evaluate the acceptability of the treatment in this population, to assess the intra and inter-individual variability of the neurophysiological procedures proposed in this study protocol, and to assess the robustness of the evaluation criteria. The results will serve as hypothesis for the sample size calculation of a larger placebo controlled trial.

4.1 Primary objective

4.1.1 Primary and secondary evaluation endpoints

4.1.1.1 Primary evaluation endpoint

The primary endpoint is the change between baseline and end of the study of each following electrophysiological criteria of demyelination measured on 8 nerves:

- motor nerve conduction velocity,
- distal latency,
- F wave latency,
- length of motor nerve potential,

A 10% improvement for 2 out of these 4 criteria, in at least 3 out of 8 nerves will be considered as clinically meaningful.

4.1.1.2 Secondary evaluation endpoints

Secondary endpoints will be part of exploratory analyses. They will consist in studying mean change or proportions for the following clinical and electrophysiological parameters.

Clinical endpoints:

- ONLS
- Timed 10-meter walk test
- MRC

- INCAT sensory score
- 6-minute walk test
- Posturometry

Electrophysiological testing endpoints:

- Supernormality (%)
- Strength-duration time constant (ms)
- Rheobase (mA)
- Refractoriness (%)
- Min-max absolute refractory period (ms)

4.2 Secondary objective

The secondary objective will evaluate the safety of MD1003.

Safety of MD1003 will be assessed by recording of adverse events in the three groups of patients.

Laboratory testing (haematology and biochemistry safety panel) will also be used to detect any drug intolerance. The following parameters will be measured at prior first administration and after 12 months of treatment:

- RBC, WBC, platelets
- Ionogram, creatinin, glycemia
- AST, ALT, bilirubin, GGT, alkaline phosphatase
- Triglyceride, cholesterol
- aPTT, INR

5 INVESTIGATIONAL PLAN

5.1 Overall study design

5.1.1 Methodology

5.1.1.1 Experimental plan

This pilot, open label, uncontrolled monocentric study is stratified a priori to recruit 5 patients per etiologic diagnosis group.

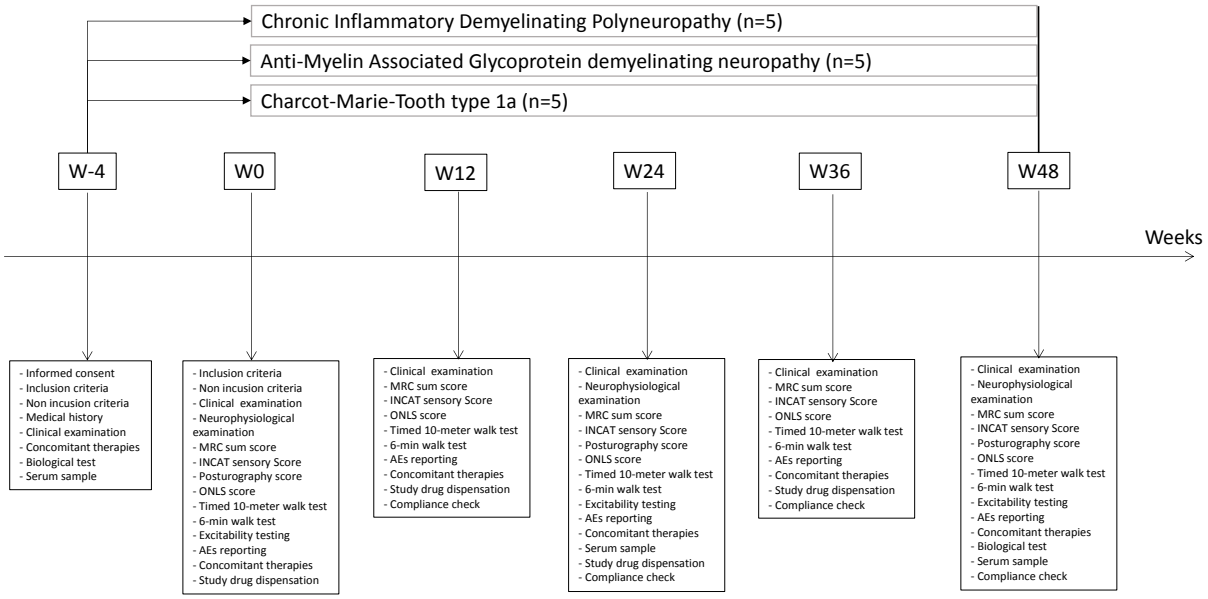
5.1.1.2 Number of centers

This study is a monocentric study.

The investigational centre's address is:

HOSPITAL HENRI MONDOR
51, AVENUE DU MARECHAL DE LATTRE DE TASSIGNY
94010 CRETEIL CEDEX

5.1.2 Study flow chart



5.2 Approximate number of patients

The study will include 15 patients in total divided into 3 subgroups of 5 patients suffering from either CIDP, anti-MAG or CMT1a or CMT1b.

5.3 Selection and withdrawal of patients

5.3.1 Inclusion criteria

Patients must fulfill all the following criteria:

- Male and female aged between 20 and 85 years.
- Patients fulfilling one of the following diagnosis:
  - Five patients with chronic inflammatory demyelinating polyneuropathy on both clinical and neurophysiological grounds.
  - Five patients with proven genetic diagnosis of CMT1a or CMT1b
  - Five patients with anti-MAG polyneuropathy.
- Electrophysiological parameters worsening for the past 3 years
- Available EMG record, performed during the past 6 months to assess variability of NCV parameters
- Signed and dated written informed consent to participate in the study in accordance with local regulations
- Likely to be able to participate in all scheduled evaluation and complete all required study procedures,
- In the opinion of the investigator, the patient will be compliant and have a high probability of completing the study.

- Both male and female subjects 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 **TWO** highly effective method of birth control for the duration of the study and for two months after the treatment termination. A highly effective method of birth control is defined as those which result in a low failure rate (i.e., less than 1% per year) when used consistently and correctly such as implants, injectable or combined oral contraceptives, IUDs, sexual abstinence or vasectomized partner. Acceptable forms of effective contraception include:

- Established use oral, injected or implanted hormonal methods of contraception.
- Placement of an intrauterine device (IUD) or intrauterine system (IUS).
- Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. Notice that, when used alone, the diaphragm and condom are not highly effective forms of contraception.
- The use of additional spermicides does confer additional theoretical contraceptive protection. Spermicides alone are inefficient at preventing pregnancy when the whole ejaculate is spilled. **Therefore, spermicides are not a barrier method of contraception and should not be used alone.**
- True abstinence: When this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Male sterilisation: subjects must present with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate. For female subjects on the study, the vasectomised male partner should be the sole partner for that subject.

5.3.2 Non-inclusion criteria

- Any general chronic handicapping disease other than peripheral neuropathy
- Impossibility to perform the 10 meters walking test
- Impossibility to assess electrophysiological parameters
- Patients with uncontrolled hepatic disorder, renal or cardiovascular disease, or cancer,
- Patients with hypersensitivity to MD1003 excipients (lactose)
- Laboratory tests out of normal range according to the reference laboratory values. Deviations may be accepted if considered by the investigator as not clinically significant with regards to the study continuation,
- Patients with history or presence of alcohol abuse or drug addiction,
- Patients likely to be non-compliant to the study procedures or for whom a long-term follow-up seems to be difficult to achieve.
- Any new medication for neuropathy initiated less than 3 months prior to inclusion.
  For CIDP patients, relapse in the past 3 months before inclusion
- Not easily contactable by the investigator in case of emergency or not capable to call the investigator
- Subjects without effective contraception

5.3.3 Patient identification and assignment of patient's 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 comes to be transferred to another site. A patient who is screened but not randomized may be re-screened at a later time. A screening number must never be reassigned for any reason. The investigator must maintain a patient master log linking the patient's 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's number will be done at the first visit (V1/selection) in chronological order of signature of the informed consent form. Once patient numbers are assigned, they cannot be reassigned. Information on the randomization number and treatment number for the whole study will be given by the investigator. The patient's initials (the first letters of the patient's name and first name) may be collected in the CRF.

5.3.4 Screen failures

Patients who sign an informed consent form but fail to meet the eligibility criteria are defined as screen failures. For all screen failures, the investigator is asked to maintain a screening log that documents the screening number (patient's number), patient's initials and reason(s) for screen failure. 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 screen failures.

5.3.5 Withdrawal of participation or arrest of treatment of an included patient

5.3.5.1 Withdrawal by the patients

Participation in the study is voluntary. The patients have the right to withdraw from the study at any time for any reason. If a patient chooses to withdraw, he must inform the Investigator immediately.

5.3.5.2 Reasons for treatment arrest

The Investigator has the right to terminate the treatment of any patient at any time if it is deemed to be in the patient's best interest.

Main reason for premature treatment discontinuation is the occurrence of a Serious Adverse Event (SAE) attributed to the treatment; the investigator must inform the sponsor of these SAE and follow them until resolution.

The reasons and circumstances for premature treatment discontinuation will be documented in the patient's CRF at time of withdrawal.

It is important to distinguish the following situations:

- Temporary cessation of treatment, the investigator must document the reason(s), the stop date and the restart date
- Early termination of treatment. In this case, the investigator must:
    - Document the reason(s) of early termination (effectiveness or failure of treatment), SAE (s), non-compliance of the patient to visits, other medical problems, patient personal reasons)
    - Make every effort to convince the patient to have a last visit to evaluate at least safety data and if possible efficacy data.
    - Make every effort to convince the patient to have a safety follow-up in the case of AE.
- Subject lost to follow-up: it is not known what became of the subject. The investigator must:
    - Make every effort to reconnect with the subject in order to know at least if the subject is alive or dead

If the subject is contacted:

- Document the reason(s)
- Offer to realize at least an evaluation of safety and if possible of efficacy, if the subject agrees

In case of the withdrawal or lost to follow-up of a subject, the data may be used in the absence of opposition of the subject. Explicit withdrawal of consent is a particular situation, where the subject clearly expresses that he withdraws the consent he signed. In case of consent withdrawal, data on the subject cannot be used unless the subject expresses no objection to their use in writing. In practice, the subject leaves the trial.

The subject may be withdrawn from the trial for several reasons, such as: the subject's condition worsens, the subject has a serious adverse effect, other medical problems, personal reason of the subject (family, work ...), without the patient withdrawing his consent.

The CRF must document the different possible reasons of withdrawal of a subject:

- Serious adverse event,
- Decision of the patient

- Poor compliance to the treatment
- Other medical problem
- Personal reasons from the subject

5.3.5.3 Follow up of patients withdrawn from the study

The withdrawal of a patient from the study will in no way impact his/her usual treatment and follow-up for the disease by his/her referring physician.

Patients withdrawn from the study will be asked to undergo a physical examination on the same dates as those scheduled in the study.

Should a serious adverse event occur resulting in withdrawn of the patient from the study by the principal investigator, the patient will be asked to be followed for a duration that will be determined by the principal investigator depending on the nature and severity of the SAE.

5.3.6 Study suspension, termination and completion

The sponsor may suspend or terminate the study or part of the study at any time for any reason.

If the investigator suspends or terminates the study, the investigator will promptly inform the sponsor or designee and the IRB/IEC and provide them with a detailed written explanation. The investigator will also return all investigational product bottles, and other study materials to the sponsor.

Upon study completion, the investigator will provide the sponsor, IRB/IEC, and regulatory agency with final reports and summaries as required by regulations.

In case of premature discontinuation of the study, the sponsor will inform in writing, all investigators, Ethics Committees and Regulatory Authorities about the reasons for cancelling the study.

When 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 products or as soon as possible thereafter.

An effort must be made to determine why a patient is lost to follow-up for the subject's CRF. A registered letter should be sent to document this effort if other attempts to contact the patient fail.

5.4 Investigational products administration

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

5.4.1 Description of investigational medicinal products

Capsules (MD1003, dose 100 mg) are taken orally three times a day (one in the morning, one at noon, and one in the evening) with or without food. Capsules should be swallowed with a glass of water.

The biotin capsules will be supplied by MEDDAY SA.

5.4.1.1 Investigational Medicinal Product

Investigational drugs units will be supplied by MEDDAY SA or designee.

The investigational drug will consist in capsules of biotin 100 mg and excipients (lactose, magnesium stearate, croscarmellose sodium, Silica).

Precaution for use:

Some laboratory tests may potentially be distorted by this medicine. These are tests that require the use of a biotin-based reagent (hormonal dosages, tumor, cardiac, anaemia, bone metabolism and inflammation markers, testing for antigen and antibodies to viral infectious diseases, tissue pathology examination). A non-exhaustive list of these parameters is displayed in Appendix 1.

An information patient card will be given to all patients regarding this precaution for use.

For additional information, investigators may connect at www.medday-lab.com

5.4.1.2 Dose regimen

The dose regimen will be 1 capsule three times a day (one in the morning, one at noon and one in the evening).

5.4.2 Packaging and labelling

MEDDAY SA or designee will prepare and ship investigational product to the study pharmacist. Each investigational product packaged in plastic bottles will be labelled according to regulation. For all patients, the treatment will be dispensed by the hospital pharmacy in boxes containing the quantity of bottles needed to cover the period until the next visit.

Capsules will be conditioned in plastic bottles containing 90 capsules each corresponding to one month of treatment.

A label with legal requirements will be stuck on the bottles with a space allowing pharmacist to indicate the patient's number and the treatment period.

5.4.3 Treatment assignments

All patients will be assigned to receive active drug 300 mg/day, open label, one capsule in the morning, one capsule at noon and one capsule in the evening.

5.4.4 Investigational product shipping, handling and storage

The investigational product will be shipped directly to the pharmacist/dispenser designated by the Investigator after required regulatory and legal documents have been received by the sponsor or designee.

Upon receipt of the investigation products, the pharmacist will verify the condition of the study supplies, including inspection of document per instructions in the Pharmacy Binder. There is no specific requirement regarding temperature during shipment for this study.

The sealed investigational product bottles must not be opened until they are used for administration.

Once unpacked and inspected, investigational products must be stored at room temperature.

The pharmacist must store the sealed investigation products in a secured area with access restricted to authorized personnel only.

The investigational product 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 investigational product must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product.

Once the investigational products have been allocated and dispensed to the patient, the investigational products must be maintained at room temperature.

Once opened the bottles containing 90 capsules each may be used for 1 month.

5.4.5 Treatment compliance, accountability and return of therapeutic units

Regulatory agencies require accounting for the disposition of all investigational drugs (IMP and NIMP) received by each clinical site. Information on drug disposition required by law consists of the date received; date administered, quantity administered, and the patient to whom the drug was allocated and dispensed. The investigator is responsible for the accounting for all unused investigational products and all used investigational product containers through the pharmacist. The pharmacist 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 investigational products must be returned to the sponsor/contract distribution center with the appropriate form.

Investigational products will be administered by the pharmacy and the date of the administration will be documented in the patient's record in addition to the CRF.

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

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

5.4.6 Destruction

Remaining test medication and packaging of used and non-used investigational medicinal products will be returned to MEDDAY 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 finalisation of the clinical trial and the compilation of the final study report.

5.5 Concomitant treatments

Any drug(s) that are NOT suspected of causing the event or reaction and that are administered to the patient AT THE TIME the case is reported should be listed as concomitant medication.

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

All usual treatments are authorized all along the study for patients already treated by these drugs. All drugs have to be introduced at least three months prior to inclusion. Introduction of any of these drugs during the trial should be avoided, and if absolutely necessary, should be documented in the CRF.

All medications will be recorded into the CRF and the patient's source documents.

If the patient used to follow a continuous physical therapy program at least the month prior to inclusion, this program should be maintained throughout the period of the study and should not be discontinued. Intensive physical therapy program should be avoided as much as possible within the 3 months prior to inclusion and during the trial since it may modify EVALUATION CRITERIA values.

5.6 Visits schedule and evaluations

5.6.1 Patient follow-up schedule

	Week -4	Week 0	Week 12	Week 24	Week 36	Week 48
	Selection	Inclusion	Follow-up			End
STUDY WINDOWS		+/-5 days	+/-10 days			+/- 15 days
Informed consent	X					
Inclusion criteria	X	X				
Non-inclusion criteria	X	X				
Medical history	X					
Clinical examination	X	X	X	X	X	X
Neurophysiological examination		X		X		X
MRC sum score		X	X	X	X	X
INCAT sensory Score		X	X	X	X	X
Posturography score		X		X		X
ONLS score		X	X	X	X	X
Timed 10-meter walk test		X	X	X	X	X
6-min walk test		X	X	X	X	X
Excitability testing		X		X		X
AEs reporting		X	X	X	X	X
Concomitant therapies	X	X	X	X	X	X
Biological test [1]	X [2]					X
Serum sample	X			X		X
Study drug dispensation		X	X	X	X	
Compliance check			X	X	X	X

[1] *Biological safety panel includes: RBC, hemoglobin, mean corpuscular volume, WBC, platelets, electrolytes (Na, K, HCO3, Ca), protein, creatinine, glomerular filtration rate, fasting blood glucose, AST, ALT, total and free bilirubin, gamma glutamyl transferase, alkaline phosphatase, triglyceride, cholesterol, PT, aPTT, INR*

[2] *Biological aetiology additional panel: Serum protein electrophoresis, IgA measurement, HbA1c, HBsAg, HIV, HCV tests, fibrinogen*

5.6.2 Pre-inclusion visit - Visit 1 (W-4)

During the pre-inclusion visit, the investigators will check inclusion, non-inclusion criteria and obtain informed consent for study participation.

The following study procedures will be carried out during the screening and the following information will be recorded into the CRF:

- Demographic data
- History of the patient's disease
- Relevant other medical history and ongoing concomitant diseases
- Vital signs: Systolic and diastolic blood pressure, temperature, heart rate
- Clinical examination
- Neurophysiological examination
- MRC sum score
- INCAT sensory Score

- Posturography score
- ONLS score
- Timed 10-meter walk test
- 6-min walk test
- Excitability testing
- Biological testing including:
    - Safety panel: RBC, hemoglobin, mean corpuscular volume, WBC, platelets, electrolytes (Na, K, Cl, HCO3), protein, creatinine, glomerular filtration rate, fasting blood glucose, AST, ALT, total and free bilirubin, gamma glutamyl transferase, alkaline phosphatase, triglyceride, cholesterol, PT, aPTT, INR
    - Aetiology additional panel: Serum protein electrophoresis, IgA measurement, HbA1c, HBsAg, HIV, HCV tests, fibrinogen
    - For women of childbearing potential: highly sensitive pregnancy test (HCG)
- Concomitant therapies

The investigator will assign a patient number starting from 01, in chronologic order of patient's inclusion.

5.6.3 Inclusion visit and randomization – Visit 2 (W0)

The investigators will check again for inclusion and non-inclusion criteria and will record following information into the CRF:

- Clinical examination
- Neurophysiological examination
- MRC sum score
- INCAT sensory Score
- Posturography score
- ONLS score
- Timed 10-meter walk test
- 6-min walk test
- Excitability testing
- AEs reporting
- Concomitant therapies
- Study drug dispensation

The investigator will fill a "drug delivery form" for the hospital pharmacy to dispense study medication. The number of treatment delivered and written on the bottles' label by the pharmacist will be the patient's inclusion number.

The patient will be supplied with the study drugs dispensed by the hospital pharmacy and advised to open one bottle per month of treatment. Each kit will contain three bottles for a total of three months of treatment. The patient will be asked to use only one bottle of 90 capsules per month and to take from this bottle one capsule in the morning, one capsule at noon and one capsule in the evening. Capsules have to be swallowed with a glass of water.

Women of childbearing potential will be provided with 3 urinary pregnancy tests to be used at home every month until next visit to eliminate any risk of pregnancy during the study.

5.6.4 Visit 3 (W12 ± 10 days)

The investigators will record the following information into the CRF:

- Clinical examination
- MRC sum score
- INCAT sensory Score
- ONLS score
- Timed 10-meter walk test
- 6-min walk test
- AEs reporting
- Concomitant therapies
- Study drug dispensation

The investigator will provide patient with a drug delivery form for the hospital pharmacy.

The patient will be supplied with the study drugs dispensed by the hospital.

Women of childbearing potential will be provided with 3 urinary pregnancy tests to be used at home every month until next visit to eliminate any risk of pregnancy during the study.

5.6.5 Visit 4 (W24 ± 10 days)

The investigators will record the following information into the CRF:

- Clinical examination
- Neurophysiological examination
- MRC sum score
- INCAT sensory Score
- Posturography score
- ONLS score
- Timed 10-meter walk test
- 6-min walk test
- Excitability testing
- AEs reporting
- Concomitant therapies
- Serum sample
- Study drug dispensation
- Compliance check

The investigator will provide patient with a drug delivery form for the hospital pharmacy.

The patient will be supplied with the study drugs dispensed by the hospital.

Women of childbearing potential will be provided with 3 urinary pregnancy tests to be used at home every month until next visit to eliminate any risk of pregnancy during the study.

5.6.6 Visit 5 (W36 ± 10 days)

The investigators will record the following information into the CRF:

- Clinical examination
- MRC sum score
- INCAT sensory Score
- ONLS score
- Timed 10-meter walk test
- 6-min walk test
- AEs reporting
- Concomitant therapies
- Study drug dispensation

The investigator will provide patient with a drug delivery form for the hospital pharmacy.

The patient will be supplied with the study drugs dispensed by the hospital pharmacy.

Women of childbearing potential will be provided with 3 urinary pregnancy tests to be used at home every month until next visit to eliminate any risk of pregnancy during the study.

5.6.7 Last visit – Visit 6 (W48 ± 15 days)

The investigator will record the following information into the CRF:

- Clinical examination
- Neurophysiological examination
- MRC sum score
- INCAT sensory Score
- Posturography score
- ONLS score
- Timed 10-meter walk test
- 6-min walk test
- Excitability testing
- AEs reporting
- Concomitant therapies
- Biological safety panel testing:
    - RBC, hemoglobin, mean corpuscular volume, WBC, platelets, electrolytes (Na, K, Cl, HCO3), protein, creatinine, glomerular filtration rate, fasting blood glucose, AST, ALT, total and free bilirubin, gamma glutamyl transferase, alkaline phosphatase, triglyceride, cholesterol, PT, aPTT, INR
    - For women of childbearing potential: highly sensitive pregnancy test (HCG)
- Serum sample
- Compliance check

5.6.8 Duration of the study

Duration of the inclusion phase: 12 Weeks

Duration of baseline period: 4 Weeks

Duration of treatment: 48 Weeks

Total duration of the trial: 64 Weeks

The end of the study corresponds to the end of the treatment's duration of the last patient included.

5.7 Efficacy evaluations

5.7.1 Main evaluation of efficacy: description and methods

5.7.1.1 Neurophysiological examination

This examination will be performed according to specific centre protocol as described below according to initial diagnosis and patient status.

Overall the four limbs will be investigated, including one motor and one sensitive nerve for a total of maximum 8 nerves. The same protocol will be applied at each visit for one patient, aiming to record on the same nerves the studied demyelination criteria.

The investigator will be free to define the most relevant protocol according to patient disease status at baseline. However, the same protocol will be applied in a patient all along the study and the investigator will apply his best efforts to comply with this rule.

5.7.1.1.1 Polyneuropathy protocol:

1. Test most involved limb first if mild; if severe do least involved limb first.
2. Test at least 2 limbs, upper and lower, do 3rd limb for symmetry.
3. Lower extremity do sural sensory, peroneal motor with conduction, tibial motor with an F-wave.
4. Upper extremity do a sensory either median or ulnar, also a motor either median or ulnar with conduction and an F-wave.

5.7.1.1.2 Polyradiculopathy protocol

1. Sural sensory ankle; stimulate 14 cm proximal to recording electrode.
2. If sural equivocal or technically difficult:
    a. Opposite sural
    b. Median sensory (index); stimulate at wrist and elbow.
3. Peroneal motor (EDB); stimulate at knee and ankle with F-response latency.
4. Tibial motor (abductor hallucis brevis); stimulate knee and ankle with F-response latency.
5. Ulnar motor (hypothenar); stimulate at wrist and elbow with F-response latency.
6. If clinically indicated, consider:
    a. Median (thenar); stimulate at wrist and elbows with F-response latency.
    b. Musculocutaneous (biceps brachii); stimulate at axilla.
    c. Facial (orbicularis oculi); stimulate at ankle of jaw.

d. Trigeminal (orbicularis oculi); stimulate supraorbital nerve.

Electrophysiological measures will be performed at W0, W24 and W48 and following parameters will be recorded in the CRF:

- motor nerve conduction velocity,
- distal latency,
- F wave latency,
- length of motor nerve potential

5.7.1.2 Excitability testing

Nerve excitability testing is a non-invasive approach in investigating the pathophysiology of peripheral nerve disorders, which determines the electrical properties of the nerve membrane at the site of stimulation

5.7.1.3 Medical Research Council (MRC) sum score

This score is a summation of the strength of 6 muscle groups tested on both sides according to the Medical Research Council (MRC) scale; it yields the so-called "MRC-sum score," ranging from 0 (total paralysis) to 60 (normal strength).

Good validity and interobserver reliability for this scale have been demonstrated in patients with Guillain–Barré syndrome and other neuropathies (Kleyweg 1991).

The score is the sum of the MRC score of 6 muscles (3 at the upper and 3 at the lower limbs) on both sides, each muscle graded from 0 to 5. The following muscles are examined:

- Deltoid
- Biceps
- Wrist extensor
- Ileopsoas
- Quadriceps femoris
- Tibialis anterior

The MRC sum score will be assessed at each visit and recorded in the CRF.

5.7.1.4 INCAT sensory Sum Score (ISS)

The Inflammatory Neuropathy Cause and Treatment (INCAT) Group introduced the ISS and extensively evaluated it in patients with immune mediated polyneuropathies (Merkies 2000)

This sensory scale comprises pin prick and vibration sense plus a two point discrimination value in the arms and legs, and ranges from 0 ("normal sensation") to 20 ("most severe sensory deficit").

The scale is displayed in appendix, will be completed at each visit and the result recorded in the CRF.

5.7.1.5 Posturography score

Computerized dynamic posturography (CDP) is a non-invasive specialized clinical assessment technique used to quantify the central nervous system adaptive mechanisms (sensory, motor and central) involved in the control of posture and balance, both in normal and abnormal conditions. Due to the complex interactions among sensory, motor, and central processes involved in posture and balance, CDP requires different protocols in order to differentiate among the many defects and impairments which may affect the patient's posture control system. Thus, CDP challenges it by using several combinations of visual and support surface stimuli and parameters.

Center of gravity (COG) is an important component of balance and should be assessed when evaluating someone's posture. COG excursion and velocity are recorded through computerized recording. COP excursion is defined by Collins & De Luca (1993) as the displacement in the anterior/posterior and medial/lateral directions within the base of support (perimeter around the feet).

Body sway during quiet upright stance will be recorded at 40 Hz using a force platform (Posturolab 40/16, Columbus, Ohio); each trial will last for 51.2 sec and, during this period, subjects will be asked to stand upright and barefoot on the platform as still as possible with arms at their sides. Recordings will be made under 4 conditions, while adding or not a layer of foam rubber (5 cm thick, density of 2.5 pcf) to the base of support, with the eyes either open or closed: condition 1 = hard surface and eyes open; condition 2 = hard surface and eyes closed; condition 3 = soft surface and eyes open; condition 4 = soft surface and eyes closed. Before each trial, the feet will be positioned according to the manufacturer reference, and small adjustments will authorize to make online; recordings with the eyes closed will be obtained just after acquiring the data with the eyes open, without moving the feet (Herrera-Rangel 2014).

The test will be performed at each visit; length (mm) and area (mm^2) of sway will be recorded in the CRF for each of the four conditions.

5.7.1.6 Overall Neuropathy Limitation Scale (ONLS)

The Overall Neuropathy Limitations Scale (ONLS), was derived by modifying the Overall Disability Sum Score (ODSS) slightly.

The ODSS focuses on upper and lower limb functions, and consists of a checklist for interviewing patients. It is scored from 0 to 5 on the upper limb section and from 0 to 7 on the lower limb section. A score of 0 indicates no limitations (the ceiling of the scale) and a score of 5 or 7 indicates no purposeful movement.

To reduce a possible ceiling effect, Graham et al. have modified the ODSS to include climbing stairs and running. Specifically, the ODSS item ‘‘Does the patient have difficulty walking?’’ has been supplemented with ‘‘Does the patient have difficulty running or climbing stairs?’’ on the new measure, the Overall Neuropathy Limitations Scale. Therefore, to score 0 (indicating no limitations) on the lower limb section of the ONLS, the patient must now have no difficulty running or climbing stairs, in addition to walking. The remaining scoring criteria are not different from those in the ODSS.

The simplicity of the ODSS is shared by the ONLS, but the ONLS has better content validity and less ceiling effect, which may make it more useful for clinical practice and research (Graham 2006).

The reliability of this scale is substantial in CMT patients (Solari 2007).

The ONLS is displayed in appendix, and will be recorded in the CRF at each visit.

5.7.1.7 Timed 10-meter walk test

In this test the patient is instructed to walk at a comfortable, normal pace for 10 meters. Only the middle 6 m, however, is timed to eliminate the effects of acceleration and deceleration. Start and stop of performance time coincides with the toes of the leading foot crossing the 2-m mark and the 8-m mark, respectively. From these data, the speed may be calculated by dividing the middle 6 m by the time (in seconds) required to walk the 6 m (Wolf 1999).

The reliability of this test is excellent for CMT patients (Solari 2007).

A full instruction for the realisation of the test is displayed in appendix. The test will be performed and result recorded in the CRF at each visit.

5.7.1.8 6-min walk test

The 6MWT is a practical simple test that requires a 30 m (100-ft) hallway but no exercise equipment or advanced training for technicians. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes. The patient is allowed to self-pace and is encouraged every two minutes by the examiner as he traverses back and forth along a marked walkway.

The reliability and validity of this test has been investigated extensively as it has been used as a functional outcome measure for adults with cardiopulmonary dysfunction. (American Thoracic Society statement: guidelines for the 6MWT, 2002). It has also been used as a functional outcome measure for individuals with multiple sclerosis (Goldman et Al 2008).

The test is more extensively described in appendix and will be performed and recorded in the CRF at each visit.

5.8 Safety evaluations

At each visit, the presence of all serious Adverse Drug Reactions (ADR) will be notified into the CRF and immediately reported to sponsor in the SAE form. SAE/ADR will immediately be reported to the Pharmacovigilance Unit of the sponsor.

5.8.1 Rating table of adverse events

Safety will be evaluated by vital signs, physical examination (including neurological examination), and biological signs. The following safety endpoints will be checked and recorded in the CRF:

- Adverse events presence,
- Vital signs including heart rate, blood pressure and weight.
- Clinical examination abnormalities,
- Standard laboratory testing abnormalities.

5.8.2 Safety endpoints

Standard clinical and adverse event monitoring will be done at each visit.

Standard laboratory testing (plasma biochemistry and haematology) will be done at W0 and W48 and consists in measurement of:

- Safety panel: RBC, hemoglobin, mean corpuscular volume, WBC, platelets, electrolytes (Na, K, Cl, HCO3), protein, creatinine, glomerular filtration rate, fasting blood glucose, AST, ALT, total and free bilirubin, gamma glutamyl transferase, alkaline phosphatase, triglyceride, cholesterol, PT, aPTT, INR

6 ADVERSE EVENTS

6.1 Definitions

Adverse Event (AE):

Any untoward medical occurrence in a 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 a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product.

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

- Abnormal test findings (see definition below)
- Clinically significant symptoms and signs
- 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 investigational product, but is considered to be related to the research conditions, i.e., related to the fact that a patient is participating in the study.

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.

Important:

All AE/SAE occurring in the study associated or not to the study drug shall be notified to the Sponsor Pharmacovigilance Unit.

Suspected Unexpected Serious Adverse Reaction (SUSAR) suspected to be related to an interaction between an IMP and a NIMP should be reported.

Medication Errors:

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

- The administration of an unassigned treatment.
- An investigational medicinal product temperature excursion not approved by the Sponsor's clinical pharmacy or designee.
- 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) on the CRF (refer to Adverse Event Reporting section for further details).

6.2 Handling of Non-Serious Adverse Events

All AEs encountered during the clinical study will be reported on the CRF.

- 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 CRFs. During the active reporting period specified above, all AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. 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 CRFs 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 CRF page.

The information to be entered in the CRF 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)

6.2.1 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.

6.2.2 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 IMP seems probable because of such factors as a clear temporal association with the use of the IMP, 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 IMP 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 are essential for a proper assessment or the additional data are under examination.

Unassessable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Not related: Not suspected to be reasonably related to the IMP. 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 CRF, 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 CRF. 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.

6.3 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 Sponsor or its designated representative.

All adverse events encountered during the clinical study must be reported on the CRF 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 CRF and the SAE form (available from the CRF web site or from the Investigator's study files).

ALL SAEs occurring during this study 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:

Pharmacovigilance Department

Fax: 33 (0)1 85 08 02 23

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, MEDDAY can be contacted at:

frederic.sedel@medday-pharma.com

guillaume.brion@medday-pharma.com

6.4 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.

In case of occurrence of SAEs attributable to experimental treatment, the DMSB will be seized by the investigator and / or sponsor to decide on the continuation of the trial.

7 STATISTICAL CONSIDERATIONS

7.1.1 Determination of sample size

This pilot study is exploratory. The various clinical and electrophysiological endpoints will allow defining which of them will be the most relevant in confirmatory randomized controlled trials.

It is assumed that 15 patients is a sufficient sample size for 1) detect an effect of MD1003 in demyelinating peripheral neuropathies, and 2) rank the best endpoints for confirmatory studies in the three most common demyelinating peripheral neuropathies.

7.1.2 Definition of populations for analysis

Safety population

All patients who receive at least one dose of study medication will be included.

Intent-to-treat population (ITT)

All patients who receive at least one dose of study medication and with at least one assessment at baseline and during the study will be included.

All analyses will be according to the intent-to-treat principle (all patients will be analysed).

Per Protocol population (PP)

All patients of the ITT and without major protocol deviations.

7.1.3 General considerations

Descriptive analyses will be performed.

Data will be 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 %). No imputation will be performed on missing data.

The analyses described below are those intended to be performed based on an estimate of the available data. If the applicable data is not available; the analyses will be adapted accordingly.

The analyses described below are those intended to be performed based on an estimate of the available data. If applicable data are not available; the analyses will be adapted using the Last Observation Carried Forward (LOCF) imputation method.

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

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

All analyses will be conducted on the ITT with a global significance level of 5%.

Primary and secondary endpoints will be considered as exploratory analyses with no defined order of analysis.

7.1.4 Primary efficacy analyses

Principal analysis of the primary efficacy endpoint

The primary endpoint will be evaluated as the change from baseline to week 48 of the following criteria of demyelination:

- Motor nerve conduction velocity,
- Distal latency,
- F wave latency,
- Length of motor nerve potential.

Eight nerves will be assessed for those four criteria. Change will be considered significant when the last value is 10% improved compared to the baseline value for two out of these four parameters in at least three nerves out of eight investigated nerves.

7.1.5 Secondary efficacy analyses

The analysis of the secondary endpoints will be descriptive:

1. Change in the ONLS score;
2. Change in the MRC sum score
3. Change in INCAT sensory Score
4. Change in the posturography score;
5. Changes in the time to 25 feet walk and the 6 minutes walk test;
6. Changes in minimal and maximal duration of the absolute refractory period (in ms), in refractoriness and supernormality (in %), in strength-duration time constant (in ms) and in rheobase (in mA) for the ulnar motor nerve.

The secondary clinical endpoints will be ranked differently according to initial diagnosis:

- CIDP:
    1. ONLS
    2. Timed 10-meter walk test
    3. MRC
    4. INCAT sensory score
    5. 6-minute walk test
    6. Posturometry
- Anti-MAG group:
    1. ONLS
    2. INCAT sensory score
    3. Timed 10-meter walk test
    4. MRC
    5. Posturometry
    6. 6-minute walk test
- CMT-1a and CMT-1b:
    1. ONLS
    2. MRC
    3. Timed 10-meter walk test
    4. 6-minute walk test
    5. INCAT sensory score
    6. Posturometry

Regarding the electrophysiological testing, the secondary endpoints will be ranked as follows:

1. Supernormality (%)
2. Strength-duration time constant (ms)
3. Rheobase (mA)
4. Refractoriness (%)
5. Min-max absolute refractory period (ms)

The secondary endpoints are changes from baseline to week 48 in ONLS, MRC, INCAT, Posturometry, Timed 10-meter walk test, 6-min walk test, Min-max absolute refractory period, Refractoriness, Supernormality, Strength-duration time constant, Rheobase

Secondary objective:

The evaluation endpoint is the proportion of patients with WHO grade III adverse events.

7.1.6 Safety analyses

All treated patients will be included in the safety analysis. All safety data will be displayed and analyzed using descriptive statistical methods. No formal statistical analysis is planned.

Time of the analyses

Safety data will be reviewed on a regular basis by the DSMB.

A complete safety analysis as described below will be performed at the time the primary efficacy endpoint is analysed. After withdrawal or completion of the study by all included patients, whole or part of the safety analyses will be performed again. The details of these final analyses will be given in the SAP.

Adverse events

In general, analysis of adverse events is descriptive.

Statistical analysis and reporting of adverse events will concentrate on treatment emergent adverse events. All adverse events with an onset after the first dose of biotin up to a certain number of days (D) (inclusive) after the last dose of biotin will be considered 'treatment emergent' and will be assigned to the treatment phase for evaluation. The number of days D will be given in the SAP. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as 'treatment-emergent'. Other adverse events will be assigned either to the screening or safety follow-up, or post study phase, as appropriate.

Vital signs, physical exam, standard laboratory tests

The set of summary statistics will be n (number of patients with non-missing values), mean, standard deviation (SD), minimum, maximum, median and interquartile range, and will be n (number patient with non-missing values) and percentage (%) for continuous and categorical endpoints, respectively.

7.1.7 Analysis by subgroups

Analyses in subgroups will be performed in order to assess the homogeneity of treatment's effect as exploratory analyses.

7.1.8 Handling of missing data

Missing data due to dropouts may occur for two major classes of reasons: non-informative reasons (essentially random, e.g., a study subject moves to another city) and informative reasons (essentially non-random, and possibly related to treatment assignment or outcomes, e.g., the study subject develops intolerable side effects).

The last observation carried forward (LOCF) approach will be used to handle missingness on the primary evaluation criterion.

7.1.9 Handling of changes in planned statistical analyses

The Statistical Analyses Plan will be validated with the principal investigator prior the data base lock at which the primary efficacy endpoint will be analysed. Any later modification will be described in a complementary SAP.

8 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 or Alternate 1572 form, if required by local regulations, an equivalent).

- 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 or Alternate 1572 form and, if required by local regulations, an equivalent).
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient 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 CSA.
- If applicable, a financial disclosure form.
- A written document containing the name, location, certification number, and date of certification of the laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the statement of investigator form. The sponsor must be notified if the laboratory is changed or if any additional laboratory is to be used.
- List of normal laboratory values and units of measure for all laboratory tests required by the protocol. This is required for each laboratory to be used during the study. The sponsor/designee must be notified if normal values or units of measurement change.

9 INFORMED CONSENT

The investigator will provide for the 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 patient 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 authorised 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.

10 DIRECT ACCESS, DATA HANDLING AND RECORD-KEEPING

10.1 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 CRFs must be fully completed and include all required data. All CRF 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.

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 or Alternate 1572 form if required by local regulations, an equivalent) 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.

10.2 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 CRF, 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.

10.3 Source document requirements

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

10.4 The use and completion of electronic Case Report Forms (CRFs)

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

CRFs are implemented electronically (CRF), using third party software application that is fully validated and conforms to regulatory requirements for electronic data capture, where applicable.

The CRF enables data capture via an on-line system on a personal computer (PC).

- Designated staff at participating site shall enter data required by the protocol into the CRF.
- All access to the system is administered by the CRF 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 CRF 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 CRFs will be implemented where appropriate.

11 ADMINISTRATIVE RULES

11.1 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.

11.2 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.

11.3 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 subjects. A protocol change intended to eliminate an apparent immediate hazard to subjects 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.

11.4 Record retention in investigation centre(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.

11.5 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.

11.6 Quality control and assurance

The sponsor or designee performs quality control and assurance checks on all clinical studies that it sponsors. Before enrolling any subjects in this study, sponsor personnel or designee and the investigator review the protocol, the investigator's brochure, the CRFs 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 CRFs is verified against source documents.

11.7 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.

11.8 Study-specific committees

11.8.1 Scientific and Steering committee to be updated

Members: Dr Frederic SEDEL, Dr Guillaume BRION

***Mission*:** defining the objective, compiling the protocol, and proposing protocol amendments during the study.

Defining the general organization of the study, coordinating the information, initially determining the methodology, and monitoring implementation of the study.

Proposing management during the study taking into account the recommendations of the data safety monitoring board (DSMB), if appropriate.

11.8.2 Data Safety Monitoring Board (DSMB)

Members: Pr Philippe LECHAT, Pr Jean François DHAINAUT, Pr Richard LEVY

DSMB's mission is 1) to ensure throughout the study the safety of patients involved in the study, and 2) to preserve the scientific and ethical integrity of the study. DSMB is an advisory committee to provide the sponsor for its biomedical research advice and recommendations on the conduct of the study.

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

- 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.

In case of occurrence of SAEs attributable to experimental treatment, the DMSB will be seized by the investigator and / or sponsor to decide on the continuation of the trial.

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13 APPENDICES

Appendix 1:

Biological testing biotin may interfere with (non-exhaustive list):

ANAEMIA
Ferritin
Folate
Vitamin B12
CARDIOLOGY
CK-MB
Myoglobin
Nt-proBNP 2
Troponin I
Troponin T
HORMONES / FERTILITY
ACTH
AMH
Cortisol
C-Peptide
DHEA-s
Estradiol
FSH, LH
HCG
hGH
Insulin
PAPP-A
PlGF
Progesterone
Prolactin
SHBG
Testosterone
THYROID
Anti TG
Anti TPO
Anti-TSHr
Calcitonin
T3, FT3
T4, FT4
Tg
TSH
T-Uptake
INFECTIOUS
Ag HBe
Ag HBs
Anti-HAV
Anti-HBc
Anti-HBc IgM
Anti-Hbe
Anti-HBs
Anti-HCV 2
CMV IgG, IgM
HIV Ag p24
HIV Ag Confirm.
HIV Combi PT
HSV-1/2 IgG
Rubella IgG, IgM
Syphilis
Toxo Avidity
Toxo IgG, IgM
DRUGS
Carbamazepine
Ciclosporine
Digitoxine
Digoxine
Gentamicine
Lidocaine
Lithium
Mycophenolate
Phenobarbital
Phenytoine
Procainamide
Sirolimus
Sodium Valproate
Tacrolimus
Theophylline
Tobramycine
Vancomycine
BONE METABOLISM
Anti CCP
Beta cross Laps
Osteocalcin
PTH
P1NP
Vitamin D
ONCOLOGY
ACE
AFP
CA 125
CA 15-3
CA 19.9
CA 72-4
Cyfra 21-1
HE4
HER-2/neu
NSE
ProGRP
PSA
S100
sFlt-1
TPS
SEPSIS / INFLAMMATION
C3, C4
CRP
IgA IgE IgG IgM
IL6 IL8 IL10
LBP
Prealbumin
Procalcitonin
TNF-α
Transferrin

Appendix 2

Medical Research Council (MRC) sum score

The total MRC sum score ranges from 0 (total paralysis) to 60 (normal strength). The score is the sum of the MRC score of 6 muscles (3 at the upper and 3 at the lower limbs) on both sides, each muscle graded from 0 to 5. The following muscles are examined:

- Deltoid
- Biceps
- Wrist extensor
- Ileopsoas
- Quadriceps femoris
- Tibialis anterior

MRC-Muscle Grading Scale

Grade	Degree of Strength
5	Normal Strength
4	Ability to resist against moderate pressure throughout range of motion
3	Ability to move through full range of motion against gravity. If a subject has a contracture that limits joint movement, the mechanical range will be to the point at which the contracture causes joint restriction
2	Ability to move through full range of motion with gravity eliminated
1	A flicker of motion is seen or felt in the muscle
0	No movement

Kleyweg RP, van der Mechè FGA, Schmitz PIM. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barrè syndrome. Muscle Nerve 1991;14:1103-1109.

Medical Research Council sum Score: Grille d'évaluation

Coter chaque muscle des deux côtés selon la règle suivante:

Grade	Force
5	Force normale
4	Mouvement possible contre résistance modérée
3	Mouvement possible contre gravité. L'étendue du mouvement s'entend jusqu'au point où une contracture bloque l'articulation.
2	Mouvement possible si la gravité est neutralisée.
1	Ebauche de mouvement vue ou palpable dans le muscle
0	Aucun mouvement

	Grade	
Muscle	**Droit**	**Gauche**
Deltoide		
Biceps		
Extenseurs du poignet		
Psoas		
Quadriceps		
Jambier anterieur		
Total		
SOMME DES SCORES		

Appendix

INCAT Sensory Sum Score (ISS). The ISS ranges from 0 (normal sensation) to 20 (most severe sensory deficit) and is composed of the summation of the following sensation qualities:

- Pinprick arm grade (range 0-4)
- Vibration arm grade (range 0-4)
- Pinprick leg grade (range 0-4)
- Vibration leg grade (range 0-4)
- Two-point discrimination grade (range 0-4)

Pinprick is tested with the sharp end of an esthesiometer, subjects indicate normal or abnormal. Paresthesia, dysesthesia or hyperesthesia are to be scored as abnormal. Normal reference point: face.

Vibration sense is tested using the graduated Rydel-Seiffer tuning fork, measures obtained are compared with the reported normative threshold values.

Pinprick and vibration sense examination take place distal to proximal and only the highest extension of dysfunction of the most affected arm and leg are recorded separately for both qualities.

Pinprick sensation (sites of examination and corresponding grades)		Vibration sensation (sites of examination and corresponding grades)		Two-point discrimination (sites of examination and corresponding grades)
Arms	Legs	Arms	Legs	Index finger [K]
Normal sense	Normal sense	Normal sense	Normal sense	Normal sense
0, at index finger[A]	0, at hallux[F]	0, at index finger[A]	0, at hallux[F]	0, < 4 mm
Abnormal sense	Abnormal sense	Abnormal sense	Abnormal sense	Abnormal sense
1, at index finger[B]	1, at hallux[G]	1, at index finger[B]	1, at hallux[G]	1, 5-9 mm
2, at wrist[C]	2, at ankle[H]	2, at wrist[C]	2, at ankle[H]	2, 10-14 mm
3, at elbow[D]	3, at knee[I]	3, at elbow[D]	3, at knee[I]	3, 15-19 mm
4, at shoulder[E]	4, at groin[J]	4, at shoulder[E]	4, at groin[J]	4, > 20 mm

A,B: index finger (dorsum distal interphalangeal joint); C: ulnar styloid process; D: medial humerus epicondyle; E: acromioclavicular joint; F,G: hallux (dorsum inter-phalangeal joint); H: medial malleolus; I: patella; J: anterior superior iliac spine; K: index finger (ventral side: distal phalanx)

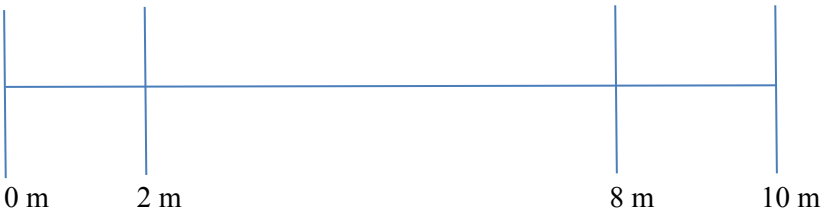
Appendix

Timed 10-meter walking test:

- The patient should be instructed to walk without assistance 10 meters (32.8 feet) and the time is measured for the intermediate 6 meters (19.7 feet) to allow for acceleration and deceleration
  - start timing when the toes of the leading foot crosses the 2-meter mark
  - stop timing when the toes of the leading foot crosses the 8-meter mark
  - assistive devices can be used but should be kept consistent and documented from test to test
- If physical assistance is required to walk, this should not be performed
- The test can be performed at preferred walking speed or fastest speed possible
- The documentation should include the speed tested (preferred vs. fast)
- Three trials have to be performed and the average of the three trials calculated

Set-up (derived from the reference articles):

- measure and mark a 10-meter walkway
- add a mark at 2-meters
- add a mark at 8-meters



Patient Instructions (derived from the reference articles):

Maximum speed trial: “I will say ready, set, go. When I say go, walk as fast as you safely can until I say stop”

> Instruction in French: « Je vais vous dire attention, prêt, partez. Lorsque je dis partez, marchez prudemment aussi vite que vous pouvez jusqu'à ce que je vous dise stop. »

Appendix

6-minute walking test Detailed instruction for challenge:

I. GENERAL INSTRUCTIONS

The Six Minute Walk Test Form is filled out by the study clinician conducting the test. Using a paper copy of the form to record the data while the test is in progress is recommended.

The Six Minute Walk, an assessment of lung function is the Flexible Block A procedure. Usually the walk should follow shortly after spirometry since it is performed after bronchodilation (for participants with COPD and/or asthma).

The testing area must be a 30m (100 ft.) segment of straight, unimpeded hallway.

Prepare the area by applying markers for the endpoints and 3m intervals to the baseboard on one side of the hall, with special attention to avoid doorways, etc.

Use the provided 30m metric tape measure. If a pre-existing 100 ft. (30.48m) course with 10ft. markers has been previously laid out, it may be used.

If available, place the traffic cones at the center of the proximal and distal turn points. Place the turn signs at the proximal and distal turn points of the course.

Have ready the following materials: stopwatch/timer, worksheet for counting laps, oximeter, Borg breathlessness and exertion scales, a chair that can be easily moved along the walking course, emergency equipment (according to local policy): telephone, sphygmomanometer, oxygen source.

A "warm-up" period before the test should not be performed.

Participants should use their usual walking aids during the test (cane, walker, etc.) and be dressed in comfortable clothing and walking shoes.

II. DETAILED INSTRUCTIONS FOR CHALLENGE

Read the following instructions to the participant:

> "The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I'm going to show you. Please watch the way I turn without hesitation."

Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly.

Record completed and partial laps on the lap count worksheet.

Say to the participant:

"Are you ready to do that? I am going to use this counter to keep track of the number of laps you complete. I will click it each time you turn around at this starting line. Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don't run or jog. Start now, or whenever you are ready."

Standardized Encouragement read in a steady voice:

- After the 1st minute: "You are doing well. You have 5 minutes to go."
- When the timer shows 4 minutes remaining: "Keep up the good work. You have 4 minutes to go."
- When the timer shows 3 minutes remaining: "You are doing well. You are halfway done.
- When the timer shows 2 minutes remaining: "Keep up the good work. You have only 2 minutes left.
- When the timer shows 1 minute remaining: "You are doing well. You only have 1 minute to go.

- With 15 seconds to go: “In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you.”
- At 6 minutes: “Stop”

If the participant stops at any time prior, you can say: “You can lean against the wall if you would like; then continue walking whenever you feel able.”

Do not use other words of encouragement (or body language) to influence the patient’s walking speed. Accompany the participant along the walking course, but keep just behind them. Do not lead them.

III. DETAILED INSTRUCTIONS FOR EACH ITEM

Before starting:

Item 1. Pulse: Record beats per minute.

Starting test:

Item 2. Start of 6-minute walk: Record time in hours and minutes. Choose AM or PM.

Immediately following 6MW: Record the following:

Item 3. Pulse: Record beats per minute.

Item 4. Breathlessness: Record participant’s response from 0-10 on the Modified Borg Scale

(0=no breathlessness, nothing at all, 0.5=very, very slight, 1=very slight, 2=slight breathlessness, 3=moderate, 4=somewhat severe, 5=severe breathlessness,6=is between severe breathlessness and very severe breathlessness, 7=very severe breathlessness, 8=between very severe breathlessness and very,very severe breathlessness, 9=very, very severe breathlessness, 10=maximum breathlessness.)

Item 5. Exertion: Record participant’s response from Scale of Perceived Exertion (0=none, 2=very,very light, 3=very light, 4=fairly light, 5=somewhat hard, 6=hard, 7=very hard, 8=very,very hard.

Item 6. Type of course used: Select the type of course used. Record 1 for 30 meters x 2 lengths, 2 for 100 feet x 2 lengths, or 3 for other. If Other, specify in the space provided.

Item 7. Record the number of completed laps

Item 8. Record the distance walked the final partial lap in meters.

Item 9. Stopped before 6 minutes: Record Y for Yes or N for No. If No skip out of form. If Yes answer Item 10 and 11.

Item 10. Duration: Record in minutes and seconds.

Item 11. Reason for stopping: Record one response 1-5. (1=desaturation <80%, 2=foot, knee, hip or other 48rthopaedic pain, 3=muscle fatigue or pain, 4=breathlessness, 5=adverse event)

Item 12. If response to Item 11=5, select all that apply. (a=angina, b=lightheadedness, c=intolerable dyspnea, d=leg cramps, e=staggering, f=diaphoresis, g=pale or ashen appearance, h=mental confusion or headache, i=other). If other is selected, please explain.

Appendix

Name:
Date:

Overall Neuropathy Limit ations Scale (ONLS)

Instructions: The examiner should question *and* observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient ha ve any symptoms in their hands or arms, eg tingli ng, numbness or weakness? ***Yes*** ☐ ***No*** ☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their hands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0= Normal
1= Minor symptoms in one or both arms but not affecting any of the functions listed ***SCORE=____***
2= Disability in one or both arms affecting but not preventing any of the functions listed
3= Disability in one or both arms preventing at least one but not all functions listed
4= Disability in both arms preventing all functions listed but purposeful movement still possible
5= Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use ***ankle foot orthoses/braces?*** (please circle)	☐	☐ ***If yes:*** (please circle) ***right/left***	

Leg grade
0= Walking/climbing stairs/running not affected
1= Walking/climbing stairs/running is affected, but gait does not look abnormal ***SCORE=____***
2= Walks independently but gait looks abnormal
3= Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4= Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm, frame)
5= Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6= Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7= Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale= arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability)) ***TOTAL SCORE=____***
Is there any disorder , other than peripheral neuropathy, which affects the above functions ***Yes*** ☐ ***No*** ☐
If ***yes*** please describe: