1. Title Page

Protocol Title:
Double Blind Placebo-Controlled Phase I/II Clinical Trial of Idebenone in Patients with Primary Progressive Multiple Sclerosis (IPPoMS)
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Total requested accrual
85 Patients
0 Volunteers

Project Uses Ionizing Radiation: ☐ No ☒ Yes
☐ Medically-indicated only
☒ Research-related only
☐ Both

IND/IDE ☐ No ☒Yes *(attach FDA documentation)*
Drug/Device/# 104,895
Sponsor: National Institute of Neurological Disorders and Stroke (NINDS), Dr. Bielekova

Durable Power of Attorney ☒ No ☐ Yes
Multi-institutional Project ☒ No ☐ Yes
Institution_____ FWA #_____
Date of IRB approval: n/a

Data and Safety Monitoring Board ☐No ☒ Yes

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Agreement type and number: Clinical trial agreement CTA#2009-0004
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Confidential Disclosure Agreement ☐ No ☒ Yes

Samples are being stored ☐ No ☒ Yes

2. Contents

3. PRECIS

3.1 Objective

The goal of this study is to assess the safety, therapeutic efficacy and mechanism of action of idebenone in primary-progressive multiple sclerosis (PP-MS) patients.

3.2 Study Population

Adult, untreated patients with PP-MS with disability ranging from none to moderately severe will be included in the trial. The upper age limit in this study has been set at 65; setting an age limit should permit us to focus on the potential neuroprotective effect of idebenone in PP-MS and limit the confounding factor of the natural aging process and its known negative influence on neuro-regeneration. Published data indicate that higher doses (10-50 mg/kg) of idebenone per day are required for beneficial effects on neurological disability in comparison to the lower doses (5-10mg/kg) that are sufficient for beneficial effects on cardiac/systemic functions in Friedreich's ataxia (FRDA) patients. Therefore, in order to target the CNS compartment, we will use a daily dose of 2250mg (750mg 3 times per day), which will provide target values of 10-50mg/kg for virtually all adult patients.

3.3 Design

This is a Phase I/II safety/efficacy trial with an adaptive trial design: one year of pre-treatment baseline period serves the dual purpose of collecting patient-specific biomarkers of disease progression and collecting longitudinal neuroimaging and clinical data for selection of primary outcome measures. This baseline period is then followed by a double-blind, idebenone versus placebo treatment phase for a total of 2 years. Based on preliminary sample size estimates, current enrollment calls for a total of 66 patients (33 per arm).

3.4 Outcome Measures

Quantitative neuroimaging measures of central nervous system (CNS: i.e. brain and spinal cord) tissue destruction and clinical and functional (i.e. electrophysiological) measures of neurological disability will be collected every 6-12 months. Additionally, biomarkers focusing on analysis of reactive oxygen species (ROS) and oxidative stress will be collected every 12 months. The trial is currently powered using progression of brain atrophy as detected by SIENA methodology as the primary outcome measure. However, this may not be the most sensitive outcome available. In recognition of this, the trial has an adaptive design: i.e. it incorporates analysis of progression of CNS tissue destruction as measured by quantitative MRI markers and clinical/paraclinical markers defined as secondary outcome measures in the first 30 enrolled patients during the one year pre-treatment baseline, before randomization. All defined outcome measures collected in the first 30 enrolled patients will be transformed into z-scores and compared for the robustness of longitudinal change over the coefficient of variation. This will permit to select the most sensitive and most accurate outcome measure for detecting progression of CNS tissue damage. As a result, the primary outcome measure of this trial will be the comparison of individualized rates of brain atrophy progression between the idebenone and placebo groups after 2 years of treatment, unless the predetermined analysis of the pre-treatment baseline period in the first 30 enrolled subjects determines that one of the predefined secondary outcome measures has a higher z-score than brain atrophy measurement. In this case, the primary outcome would be the efficacy of idebenone versus placebo in inhibiting patient-specific slopes of functional or structural deterioration as measured by this more sensitive biomarker of CNS tissue destruction, yet to be defined by the analysis of the 1-year longitudinal data from pre-treatment baseline.

4. INTRODUCTION/SCIENTIFIC RATIONALE

4.1 Multiple Sclerosis (MS)

Multiple sclerosis (MS) is an inflammatory and demyelinating disorder of the central nervous system (CNS) that destroys myelin, oligodendrocytes, axons and neurons *(Noseworthy, Lucchinetti et al. 2000)*. The vast majority of newly-diagnosed MS patients develop the relapsing-remitting form of the disease (RR-MS), in which periods of neurological worsening are followed by periods of spontaneous remission, at least at the beginning of the disease process. About 10-15% of patients develop primary-progressive MS (PP-MS), characterized by progressive accumulation of neurological disability from the disease onset, without any superimposed worsening (i.e. relapses) or improvements (remissions) *(Miller and Leary 2007)*.

The etiology of MS remains unclear, but disease develops in genetically susceptible individuals exposed to environmental triggers. The long favored hypothesis in MS has been formulated based on data obtained in the animal model Experimental Autoimmune Encephalomyelitis (EAE). This hypothesis implicates autoreactive, myelin-targeting CD4+ T cells generated in the periphery that access the CNS, where they induce an inflammatory cascade that results in the injury of previously normal neural tissues *(Sospedra and Martin 2005)*. However, in contrast to EAE, neither the target(s) of the immune response nor the cells of the immune system responsible for CNS damage have been identified in MS.

4.2 Primary progressive MS (PP-MS)

PP-MS patients differ from RR-MS patients in several important characteristics: 1. They tend to be older at the time of disease onset (mean 40 vs. 30 years); 2. Males and females tend to be affected equally; 3. Clinically there is a high prevalence of cortico-spinal dysfunction characterized by progressive weakness and spasticity; 4: Patients have more prominent involvement of the spinal cord *(Bieniek, Altmann et al. 2006)* and generally lower amount of distinct white matter lesions (i.e. plaques) in the brain and less evidence for brain inflammatory activity *(Lucchinetti and Bruck 2004)* and, most importantly: 5: PP-MS patients do not respond to immunomodulatory therapies with proven efficacy in RR-MS *(Leary and Thompson 2005)*.

However, there are also some key similarities between PP-MS, RR-MS and secondary-progressive MS (SP-MS; the disease subtype that usually evolves after several years of untreated RR-MS): 1. Age of onset of the progressive phase is virtually identical between PP-MS and SP-MS (~40 years) (Ebers 2004); 2. Genetic background (e.g. HLA and IL-7Rα association *(Booth, Arthur et al. 2005)*) seems to be common to all 3 subtypes; an observation that is further supported by the fact that different disease types can occur within a single family; 3. Patients with all MS subtypes (~90% of RR-MS and 70-80% of PP-MS patients) have evidence for humoral immune responses in the CNS that are increased compared to the serum, or are entirely specific for the intrathecal environment (i.e. increased CSF IgG index and oligoclonal bands (OCB)) *(Miller and Leary 2007)*.

These differences and similarities underlie two major hypotheses about the relationship between PP-MS and RR/SP-MS: while some authors propose these diseases are simply phenotypical variants of the identical disease process, others believe that PP-MS represents a distinct degenerative form of the disease, in which the immune response may not be primarily driving the disease pathogenesis. The latter hypothesis is indirectly supported by the "MS disease heterogeneity concept", in turn backed by pathological data indicating the mechanism of active

demyelination seems different between different patients, but identical for all MS lesions within single subjects. Four pathological subtypes have been identified *(Lucchinetti, Bruck et al. 2000)*, two of which probably represent immune-mediated pathology, whereas in the other two pathological patterns immune cells are much less conspicuous and degenerative pathophysiology may predominate *(Lucchinetti, Bruck et al. 2000)*. Specifically, pattern IV demyelination, called "oligodendrycyte degeneration in periplaque white matter", with evidence of apoptosis of oligodendrocytes and paucity of T/B lymphocytes, is almost exclusively observed in PP-MS patients. Nevertheless, PP-MS patients were also observed to have pathological patterns I and II, i.e. those where presumed mechanisms of acute demyelination are T cell/macrophage-mediated and Ab/complement-mediated, respectively.

Part of the pathophysiological controversy may reside in our inability to correctly classify patients. Complete reliance on clinical characteristics makes the classification highly dependent on the patient's ability to recollect transient neurological deficits that may have occurred years before the onset of progressive disease. Additionally, if MS lesions developed in clinically silent areas, even if associated with inflammation, they would not cause clinical deficit and therefore would not alert the patient or clinician of the occurrence of a relapse. As a result, reliance on purely clinical criteria will inevitably lead to inclusion of a more heterogeneous patient population in the PP-MS category. One of the hallmarks of inflammatory lesions in RR-MS is their association with the breakdown of the blood-brain barrier (BBB), which can be visualized as contrast-enhancing lesions (CELs) on MRI. Although PP-MS patients generally have a significantly lower number of CELs *(Ingle, Stevenson et al. 2003)*, patients with CELs have been classified as PP-MS based on clinical criteria *(Filippi, Campi et al. 1995)* and have been included in clinical trials of immunomodulatory therapies *(Wolinsky, Narayana et al. 2007)*. Not unexpectedly, it is precisely these PP-MS patients that were shown to benefit from applied immunomodulatory therapy in subgroup analysis *(Wolinsky, Narayana et al. 2007)*. This is very reminiscent of our experience with effectiveness of immunomodulatory therapies for SP-MS *(Kappos, Weinshenker et al. 2004)*. The results of these trials suggest that while currently available immunomodulatory therapies effectively target that part of the MS disease process characterized by formation of focal CELs, they are much less effective in slowing down a more diffuse, degenerative process, which underlies the development of disability in non-inflammatory PP- and SP-MS. What is the pathophysiological substrate of this more diffuse, degenerative disease process?

4.3 Mechanisms of tissue injury in PP-MS

Both new imaging modalities *(Filippi, Rocca et al. 2002, Dehmeshki, Chard et al. 2003, Filippi 2003, Narayana, Wolinsky et al. 2004, Sastre-Garriga, Ingle et al. 2004, Rovaris, Gallo et al. 2005, Sastre-Garriga, Ingle et al. 2005, Ramio-Torrenta, Sastre-Garriga et al. 2006, Khaleeli, Sastre-Garriga et al. 2007, Manfredonia, Ciccarelli et al. 2007, Rovaris, Judica et al. 2008)* and pathological data *(Lucchinetti and Bruck 2004, Kutzelnigg, Lucchinetti et al. 2005)* suggest that in PP-MS, CNS pathology is more diffuse *(Filippi, Rocca et al. 2002, Dehmeshki, Chard et al. 2003, Filippi 2003, Narayana, Wolinsky et al. 2004, Ramio-Torrenta, Sastre-Garriga et al. 2006, Khaleeli, Sastre-Garriga et al. 2007, Manfredonia, Ciccarelli et al. 2007, Rovaris, Judica et al. 2008)* and occurs to some extent independently of focal lesions *(Sastre-Garriga, Ingle et al. 2004, Kutzelnigg, Lucchinetti et al. 2005, Rovaris, Gallo et al. 2005)*. The cervical spinal cord is the major target of the disease process in PP-MS, underlying most of the clinical disability *(Ingle, Stevenson et al. 2003)*. The diffuse CNS process in PP-MS is characterized by microglial activation and diffuse axonal injury in the white matter *(Kutzelnigg, Lucchinetti et al. 2005)* and by cortical demyelination and neuronal loss in the gray matter *(Kutzelnigg, Lucchinetti et al. 2005)*.

Additionally, low level but persistent endothelial abnormalities and BBB leak, both in normal appearing white and gray matter have been observed *(Leech, Kirk et al. 2007)*.

Accumulating data indicate that oxidative stress and mitochondrial dysfunction may play a major role in the pathogenesis of MS, especially in the progressive stages *(Gionchetti, Campieri et al. 1994, Greco, Minghetti et al. 1999, Bizzozero, DeJesus et al. 2005, Dhib-Jalbut, Arnold et al. 2006, Koch, Ramsaransing et al. 2006, Koch, Mostert et al. 2007)*. MS patients have increased lipid peroxidation products in the CSF *(Hunter, Nlemadim et al. 1985, Naidoo and Knapp 1992, Keles, Taysi et al. 2001)*; presence of 3-nitrotyrosine in demyelinated lesions *(Liu, Zhao et al. 2001)*; evidence of nitrosative damage in the normal-appearing white matter *(Bizzozero, DeJesus et al. 2005)* and increased levels of carbonyl in both white and gray matter *(Bizzozero, DeJesus et al. 2005)*. These findings were recently confirmed on brain tissue derived from 18 MS patients with progressive disease (SP-MS and PP-MS), where the authors demonstrated severe oxidative damage to proteins, nucleic acids and lipids, predominantly in the MS lesions and to a milder degree also in normal appearing WM *(van Horssen, Schreibelt et al. 2008)*. In terms of cellular localization, most of the oxidized lipids, proteins and nucleic acids were detected in reactive astrocytes and in myelin-laden macrophages. Detected oxidative stress/damage was associated with strong upregulation of Nrf2/ARE-regulated antioxidant enzymes, such as superoxide dismutase-1 and -2, catalase and heme oxygenase-1. Again, these enzymes were upregulated predominantly in reactive astrocytes and foamy macrophages. These data indirectly suggest that reactive astrocytes and macrophages that phagocytosed myelin debris are the main cell types involved in detoxification of ROS and that astrocytes, through expression of Nrf2-ARE enzymes play a pivotal role in the maintenance of redox homeostasis under inflammatory CNS conditions *(van Horssen, Schreibelt et al. 2008)*. Oligodendrocytes and brain endothelial cells had remarkably low expression of antioxidant enzymes *(van Horssen, Schreibelt et al. 2008)*; a finding that supports previous studies indicating that oligodendrocytes are extremely sensitive to oxidative stress due to their impaired antioxidant defense mechanism *(Juurlink, Thorburne et al. 1998)*. Other studies suggested that MS patients may have diminished resistance to oxidative stress, as the levels of antioxidants were found to be diminished in the brain *(Langemann, Kabiersch et al. 1992, Bizzozero, DeJesus et al. 2005)* and blood *(Zagorski, Dudek et al. 1991, Syburra and Passi 1999)* of MS patients.

The respiratory burst system of activated microglia/macrophages represents one of the most abundant sources of reactive oxygen species (ROS) in the brain, in addition to the electron-transport chain of mitochondria. Mitochondria themselves may be the target of the oxidative damage in MS lesions *(Lu, Selak et al. 2000)* and profound mitochondrial dysfunction was found in the gray matter of MS patients *(Dutta, McDonough et al. 2006)*. Specifically, functional activities of mitochondrial electron transport chain (ETC) complexes I and III were decreased in MS motor cortex and this reduced mitochondrial gene expression was specific for neurons *(Dutta, McDonough et al. 2006)*. It is hypothesized that mitochondrial dysfunction, which generally increases with age, may contribute, if not underlie the development of progressive stage of MS *(Andrews, Nichols et al. 2005)*. This hypothesis is based on several published observations:

1) Acute demyelination leads to conduction block and resultant compensatory distribution of Na channels from the node of Ranvier along the entire demyelinated segment. In addition to this topographic redistribution of Na channels, demyelinated axons revert to a stage seen in immature axons, with preferential use of $Na_v1.2$ instead of $Na_v1.6$ channels *(Black, Kocsis et al. 1990)*.

2) This switch in Na channel usage and their redistribution, while allowing conduction along the demyelinated axon, is energetically extremely demanding, requiring a large number of ATP molecules to sustain the Na^+/K^+-ATPase pump, which is necessary to maintain the resting membrane potential *(Black, Kocsis et al. 1990, Black, Newcombe et al. 2007)*. This high energy demand is indirectly reflected by the observed redistribution of mitochondria along demyelinated axons *(Mutsaers and Carroll 1998)* and associated axonal swelling.
3) Presence of inflammation further exaggerates this energy deficiency of demyelinated axons, because some of the inflammatory mediators (e.g. NO) are known to inhibit the mitochondrial respiratory chain *(Bolanos, Almeida et al. 1997)*.
4) However, even in the absence of inflammation, it would be predicted that mitochondria would not be able to sustain the non-physiologically high energy demand of chronically demyelinated axons long-term. It is known that even during the natural aging process, mitochondrial DNA accumulates mutations and energy production of aging mitochondria diminishes in time. Damaged mitochondria show impairment of oxidative phosphorylation, decreased rate of electron transfer, decreased enzymatic activities and are also thought to produce higher levels of ROS. This, in the absence or deficiency of an effective endogenous detoxification system, would lead to further oxidative damage of mitochondrial DNA and associated lipids and proteins, creating a vicious cycle of mitochondrial damage. Mitochondrial DNA is especially susceptible to oxidative damage due to lack of protective histones and less efficient repair mechanisms *(Mecocci, MacGarvey et al. 1993)*.
5) The resultant lack of ATP would lead to increased intra-axonal Na^+ and subsequent increase in intra-axonal Ca^{2+} via reversal of the Na^+/Ca^{2+} exchanger. Thus, resultant damage to the demyelinated axon would be a combination of oxidative damage with Ca^{2+}-mediated excitotoxicity, leading to programmed cell death or necrosis. However, the Na^+/Ca^{2+} exchanger was found only in acutely demyelinated axons and not in chronically-demyelinated axons *(Black, Kocsis et al. 1990)*, suggesting that the mechanism of axonal damage might differ between these two conditions.

There is additional evidence that supports the hypothesis of mitochondrial dysfunction underlying axonal degeneration in MS: CSF concentrations of sorbitol, fructose and lactate (all metabolites of extramitochondrial glucose metabolism) were found to be elevated in MS, especially in progressive stages and to correlate with clinical measures of disability *(Regenold, Phatak et al. 2008)*. Because extra-mitochondrial glucose metabolism increases with impaired mitochondrial metabolism of glucose, these findings strongly implicate mitochondrial dysfunction in the pathogenesis of progressive stages of MS. Of interest to this study, the intraventricular lactate can be measured serially in-vivo by MRS *(Kaufmann, Shungu et al. 2004)*, although this methodology has not been applied to MS to our knowledge.

4.4 Therapeutic options for PP-MS patients

There are currently no treatments with proven therapeutic efficacy for PP-MS *(Leary and Thompson 2005)*. Neither interferon-beta preparations *(Leary, Miller et al. 2003, Montalban 2004)* nor glatiramer acetate *(Wolinsky, Narayana et al. 2007)* could slow down the accumulation of

disability in PP-MS. Several Phase II trials of Mitoxantrone in PP-MS were initiated, but none reported positive effects *(Leary and Thompson 2005)*. A recently reported large multi-center, placebo-controlled Phase II trial of Rituximab in PP-MS also failed to demonstrate any effect on the accumulation of disability in this patient population http://www.nationalmssociety.org/news/news-detail/index.aspx?nid=221.

These data collectively indicate that therapies targeting the immune system and specifically the formation of Gd-enhancing MS lesions do not demonstrate beneficial effect in PP-MS. In agreement with the reviewed hypothesis that the pathophysiology of PP-MS may rely more on neurodegenerative, rather than immune-mediated mechanisms of CNS tissue destruction, a pilot trial of the neuroprotective agent riluzole showed a mild effect on inhibiting the development of cervical cord atrophy in the PP-MS cohort *(Kalkers, Barkhof et al. 2002)*, which however, did not reach statistical significance.

Although the use of immunomodulatory agents in progressive MS is widespread, despite lack of demonstrated efficacy in placebo-controlled trials, the debate about such erroneous contemporary practices continues. Specifically, while individual providers argue that there may be patients with progressive MS who respond to immunomodulatory agents, the statisticians point to the fact that such responses have to be marginal in view of negative efficacy data and do not take into account side effects from these therapies and associated costs both for patients and the society (Ioannidis 2013). Therefore, use of immunomodulatory drugs for progressive MS outside of clinical trials cannot be advisable and recommendation against such use was recently endorsed by AAN among its "Top five choosing wisely" recommendations (Langer-Gould, Anderson et al. 2013).

4.5 Idebenone pharmacokinetic, pharmacodynamic and toxicity data

Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone) is a synthetic analogue of coenzyme Q10, which is an indispensable constituent of the mitochondrial electron-transport chain (ETC) and also cell membrane antioxidant.

After oral administration, idebenone undergoes rapid and extensive metabolism, whereby >99% of parent molecule is converted to metabolites by first pass metabolism. In the initial steps of metabolism, the side chain of parent idebenone undergoes a process of oxidative shortening leading to the metabolites QS-10, QS-8, QS-6 and QS-4 (the number refers to the number of carbon atoms in the side-chain). Parent idebenone and all of the short-chain metabolites are modified further by conjugation (glucuronidation or sulfatation) resulting in conjugated forms of idebenone (Idebenone-C) as well as QS-10-C, QS-8-C, QS-6-C and QS-4-C.
The bioanalytical methods allow measurement of either

- parent idebenone and unconjugated metabolites (idebenone, QS-10, QS-6, QS-4)
- or the combined measurement of conjugated molecules plus unconjugated forms of the same molecules, referred to as 'total idebenone', 'total QS-10', 'total QS-6' and 'total QS-4', respectively.

Preclinical studies

The pharmacology and toxicology of idebenone have been studied extensively in animals and humans *(Gillis, Benefield et al. 1994)*. These studies are described fully in the Investigator's Brochure (Appendix G) and are summarized below:

In rats and dogs oral idebenone is rapidly absorbed and extensively metabolized in the intestinal mucosa and liver. The primary route of metabolism is β-oxidative shortening of the side chain. The major metabolites are QS-10, QS-8, QS-6, and QS-4 (where 10, 8, 6 and 4 denote the number of carbon atoms in the side chain). Glucuronide and sulfate conjugates of these metabolites are also formed. In rats, idebenone is 91% absorbed and 90-94% protein bound. The T_{max} of parent idebenone is 0.25 hours and the half-life is 4.5 hours. In dogs, idebenone is 62% absorbed and 99% protein bound. The T_{max} is one hour and levels show a biphasic decline with half-lives of 2.2 and 15.4 hours, respectively. In dogs, dose-dependency for plasma levels was found between 10 and 100 mg/kg/day, but there were no differences between 100 and 500 mg/kg/day. There was no evidence of accumulation of idebenone or metabolites. In both rats and dogs, oral idebenone was completely excreted within 48 hours, distributed evenly between urine and feces.

The acute oral toxicity of idebenone was low (> 10,000mg/kg in mice and male rats; ~10,000 mg/kg in female rats). Chronic oral toxicity studies in rats and dogs have been published *(Spicer and Wazeter 1985, Suhara, Chiba et al. 1985)*. Treatment related adverse effects were limited to local irritant effects mainly in the forestomach (a rodent-specific organ) in the rat and to clinical gastrointestinal effects (loose feces/diarrhea and emesis), without any pathological changes, in the dog. It can therefore be considered that no adverse effects of clinical relevance were observed at the highest dose used in these studies (500mg/kg/day) *(Spicer and Wazeter 1985, Suhara, Chiba et al. 1985)*. Exposure in rats an dogs at this dose level exceeds by >3-fold the exposure in human subjects receiving a dose of 750mg idebenone tid and thus an adequate safety margin should exist at human doses up to 2250mg/day. Results from bridging toxicity studies conducted by Santhera are consistent with the findings of published Takeda studies, indicating that the drug substance used by Santhera has a similar safety profile as the Takeda material.

Idebenone was not genotoxic in *in-vitro* bacterial reverse mutation assays and *in-vivo* mouse micronucleus studies. A positive clastogenic effect was observed in an in vitro chromosome aberration test at very high concentrations (7500ng/ml and above) (RCC-CCR 871902). This effect is not considered to pose a risk for clinical trial subjects in view of the high concentrations at which effects were observed and in view of the negative in vivo response on the mouse micronucleus test.

Idebenone at doses up to 500mg/kg/day had no adverse effects on fertility and reproductive performance in rats. Idebenone administered at doses up to 500mg/kg/day in the rat and up to 150mg/kg/day in the rabbit during the period of organogenesis had no teratogenic or embryo-fetal toxic effects. Doses up to 500mg/kg/day administered during late pregnancy and lactation had no adverse effects on the dams or on the post partum development of the pups.

Clinical studies

In healthy volunteers, idebenone is well tolerated when given as single oral doses up to 1050mg (SNT-I-004) or as multiple oral doses of 2250mg/day (750mg TID) for 14 days (SNT-I-003).

Idebenone has been extensively studied as a potential therapeutic agent for neurological diseases, including Alzheimer's disease *(Gutzmann and Hadler 1998, Gutzmann, Kuhl et al. 2002)*, Huntington's disease *(Ranen, Peyser et al. 1996)*, Friedrich's ataxia (FRDA) *(Schols, Vorgerd et al. 2001, Artuch, Aracil et al. 2002, Rustin, Rotig et al. 2002, Buyse, Mertens et al. 2003, Mariotti, Solari et al. 2003, Artuch, Aracil et al. 2004, Rustin, Bonnet et al. 2004, Di Prospero, Baker et al.*

2007, Pineda, Arpa et al. 2008) and multi-infarct dementia. In these clinical trials, in which a variety of doses and dosing regimens were employed, idebenone was found to be safe and well tolerated. In phase I trials, idebenone was shown to be well tolerated at doses of 360 mg/day for 12 months, and at doses of 900 mg/day for four weeks. In a double-blind, placebo controlled trial of idebenone for the treatment of Huntington's disease, 100 patients were randomized to receive idebenone 90 mg three times per day or placebo for a period of 12 months. Ninety-one patients completed the study, and no patients left the trial for adverse events attributed to idebenone. Idebenone was found to be safe and well tolerated in this study, but no benefit was found *(Ranen, Peyser et al. 1996)*. Experience from the phase II and III clinical trials for Alzheimer's disease, in which patients received a 120 mg, 240 mg, or 360 mg three times per day for periods of up to 2 years, suggests a relatively benign toxicity profile for this drug. No therapeutic benefit was found. The most frequently cited adverse effects that occurred more often in the idebenone group were gastrointestinal symptoms such as anorexia, nausea, and diarrhea. Idebenone was marketed in Japan from 1986 to 1998 for the treatment of cognitive difficulties following stroke. During this period, idebenone was one of the most frequently prescribed drugs following stroke, with an estimated eight million patients treated. Idebenone was removed from the market in Japan after a post-marketing study failed to demonstrate efficacy, but remains registered for cognitive disorders in Italy, Portugal, Argentina and Ecuador.

No new issues of safety or tolerability have emerged in the course of the current Phase II and III clinical studies with idebenone in Friedreich's Ataxia (FRDA), Duchenne Muscular Dystrophy, and Leber's Hereditary Optic Neuropathy. Patients (8 years or older) received doses of idebenone ranging from 180 or 360 mg/day to 1350 or 2250 mg/day, depending on body weight, or placebo. Blood and urine laboratory analyses, vital signs and ECGs have not highlighted any safety concerns to date. Idebenone has been approved for the treatment of FA in Canada, is available under provisional approval for cardiomyopathy in FA in Switzerland, and can be obtained on a "named patient" basis in a number of other European countries, such as France, Italy, Belgium and Spain. Overall, more than 8 million patients have received idebenone treatment. This represents more than 59,900 patient-years experience.

Pharmacokinetics and product metabolism in humans

Four Phase I studies were performed by SANTHERA, two single-dose studies, giving 150 mg idebenone or 7x150 mg idebenone to healthy male subjects after a standardized continental breakfast (Study SNT-I-002 and Study SNT-I-004), one two-way single dose study in two groups of healthy subjects to assess the effect of a fat-rich meal on the pharmacokinetics of idebenone 150 mg or 5x150 mg (Study SNT-I-001), and a two-week repeated dose study in two groups of healthy subjects to assess the effect of repeated dosing with either 150 mg t.i.d. or 5x150 mg t.i.d. (with the morning dose being given after a standardized continental breakfast) on the pharmacokinetics of Idebenone (Study SNT-I-003). Furthermore two Phase I studies were performed at the NIH in FRDA patients *(Di Prospero, Baker et al. 2007, Di Prospero, Sumner et al. 2007)*. These studies are summarized below:

Overall conclusion of the Santhera Phase I program

Idebenone up to 1050 mg given as a single dose and up to 750 mg t.i.d (2250 mg) given as repeated doses for 14.3 days was well tolerated *(Bodmer, Vankan et al. 2009)*. The reported AEs are mainly gastrointestinal system disorders. There were no clinically relevant effects seen on hematological parameters or on biochemical parameters, in particular no effects

were observed on renal or liver function or on lipid metabolism, including HDL and LDL cholesterol.

Frequent monitoring of ECG morphology and QTc duration in studies SNT-I-001 and SNT-I-003 covering the whole time interval in which free idebenone was above the limit of quantification gave no clinically relevant abnormal findings, and in particular no prolongation of the QTc interval.

After administration, idebenone is immediately metabolized by side chain reduction to QS10, QS8, QS6, and QS4. Both idebenone and its metabolites are conjugated and then rapidly excreted, predominantly by the kidney. Parent (non-metabolized and non-conjugated) idebenone in plasma amounts to between 0.1% and 1% of total (free plus conjugated) idebenone[1], indicating a very high first-pass effect. Therefore the plasma concentrations of parent idebenone are very low even after relatively high doses. e.g. Cmax and AUC of free idebenone after dosing of 2250 mg/day for two weeks are 22.4 ng/ml and 32.2 mg/L x hr respectively. For the conjugated metabolites in the same study (SNT-I-003), Cmax and AUC are 5229 ng/ml and 32221 mg/L x hr respectively. The amount of the total metabolites QS10, QS6 and QS4 is in the same order of magnitude as that of total idebenone. The pharmacokinetics of idebenone is linear as assessed by the amounts of total idebenone. Increasing the oral dose of idebenone five or seven fold results in corresponding increases in the AUC of total idebenone.

There is a food effect, as assessed in study SNT-I-001, which is slight and more pronounced at the higher dose. Repeated daily dosing does not lead to relevant accumulation of the metabolites indicating no enzyme auto-inhibition. In addition, there is no indication that idebenone metabolizing enzymes are induced. Because of the high first pass effect, the increase of bioavailability with food is considered to be beneficial. Therefore the dosing recommendation for idebenone in all studies is for the daily dose to be given in three administrations (t.i.d.) with a meal.

Overall conclusion on the NIH Phase I program in FRDA patients

Two studies have been performed by the NIH to establish the maximum tolerated dose of idebenone in children, adolescents and adults with Friedreich's ataxia when idebenone was administered as a single oral dose (Phase I A study) or as repeated oral doses (Phase I B study).

In both Phase I studies, PK characteristics of idebenone were assessed in children, adolescents and adults. In the single dose study, doses up to 75 mg/kg were administered. In the repeated dose study a dose of 60 mg/kg was administered for 1 month. In the repeated dose study no relevant differences for Cmax and AUC for total idebenone between the age groups were detected, as shown in the table below:

Group/Dose	t_{max} (h)	C_{max} (ng/ml)	$AUC_{(0-8)}$ (h*ng/ml)	$t_{1/2}$ (h)
CHILDREN				
Mean	1.5	10927.0	57341.8	9.2
SD	0.6	1843.8	5719.0	1.0
Median	1.5	10711.0	56366.3	9.0
ADOLESCENTS				
Mean	2.8	11462.4	64717.0	10.4
SD	1.1	5045.0	20811.6	2.2
Median	2.0	9849.0	61428.9	10.2
ADULTS				
Mean	3.2	11205.6	64083.9	12.7
SD	2.7	3665.3	15306.1	4.4
Median	2.0	10225.0	60176.6	11.6

[1] Total idebenone and metabolites were analyzed after deconjugation of analytes in plasma. "Total" values therefore reflect total conjugated plus free non-conjugated analytes.

Idebenone was well tolerated. AEs reported were consistent with the known safety profile, with GI disturbances being the most frequent reported AEs for idebenone.

Studies in patients with impaired organ function

Two studies were performed in patients with impaired organ function (Reports CV2619/EC071 for hepatic; CV2619/EC070 for renal). As expected, patients with impaired renal function not undergoing hemodialysis, have higher C_{max} and AUC values of total idebenone and total QS-10 than subjects with normal renal function, but patients with impaired renal function and undergoing hemodialysis have similar exposure values of total idebenone and only slightly higher values of total QS-10 than subjects with normal renal function. These data are in agreement with the finding that the metabolites of idebenone are almost 80% eliminated by the kidney. The study also shows that total idebenone, and most probably also the other even more hydrophilic metabolites, can be eliminated by hemodialysis.

Patients with impaired hepatic function have higher exposure and longer elimination half-lives of total idebenone and total QS-10 than subjects with normal liver function, indicating that the shortening of the side chain of idebenone is impaired.

Based on the results of the two studies, it is recommended that caution be exercised in patients with impaired renal function not undergoing hemodialysis. Idebenone is contraindicated in patients with impaired liver function.

Absorption of idebenone from the Takeda formulation, used in the NIH Phase I studies, and absorption from the Santhera formulation are similar, indicating no important differences in pharmacokinetic behavior between the formulations of the trial populations. Safety and tolerability were good in the published NIH studies and in the Santhera studies. Thus clinical safety/efficacy

data and post-marketing experience available for the Takeda formulation can be considered to be relevant also to the Santhera formulation.

Product information

The study medication is manufactured by Santhera Pharmaceuticals and will be provided as 150 mg tablets with matching placebo tablets.

The active compound, idebenone, is a yellow-orange crystalline material that melts at 52 to 54ºC. Idebenone is readily soluble in organic solvents but is practically insoluble in water. It is highly stable at room temperature. The molecular weight is 338.46. The complete description of active formulation and placebo is below:

Idebenone 150 mg film-coated tablets SNT-MC17/F02
Ingredients: idebenone, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium povidone, magnesium stearate, silicon dioxide, film-coat: Opadry II 85F23495 (consisting of: aluminium lake, FD&C yellow #6, macrogol/PEG 3550, polyvinylalcohol, titanium dioxide, talc).

Placebo film-coated tablets SNT-MC17/F03
Ingredients: lactose monohydrate, microcrystalline cellulose, magnesium stearate, film-coat: Opadry II 85F23495 (consisting of: aluminium lake, FD&C yellow #6, macrogol/PEG 3550, polyvinylalcohol, titanium dioxide, talc).

Storage and handling

Idebenone tablets are supplied in high density polyethylene (HDPE) bottles, and should be stored at room temperature (15-25ºC) and must be protected from direct sunlight. Temperature excursions are permitted as follows: up to 30ºC for 12 months, up to 40ºC for 6 months.

4.6 Rationale for the use of Idebenone in PP-MS

As described above (Section 4.3: Mechanism of tissue injury in PP-MS), mitochondrial dysfunction together with aberrant formation of ROS are believed to underlie at least partially the development of progressive CNS tissue destruction in PP-MS. Idebenone has two key modes of action that make it an attractive therapeutic candidate for PP-MS:

1) Idebenone enhances the electron flow in the mitochondrial ETC. Specifically, idebenone can substitute for Coenzyme Q_{10} as an electron carrier and distribute the electrons between the various dehydrogenases and the cytochrome segments of the respiratory chain *(Sugiyama and Fujita 1985, Sugiyama, Fujita et al. 1985, Imada, Fujita et al. 1989, Geromel, Darin et al. 2002)*

2) Idebenone functions as an anti-oxidant against membrane damage caused by lipid peroxidation, including lipid peroxidation that occurs in brain mitochondria *(Suno and Nagaoka 1984, Sugiyama, Fujita et al. 1985, Suno and Nagaoka 1989, McDaniel, Neudecker et al. 2005)*.

In view of the hypothesized involvement of mitochondrial dysfunction, and particularly the reduced activity of the ETC, idebenone is a rational treatment choice in PP-MS based on its pharmacological properties. Furthermore, idebenone is known to cross the blood-brain barrier *(Torii, Yoshida et al. 1985)* and is readily taken up by cells, even those with normal Coenzyme Q_{10} content *(Geromel, Darin et al. 2002)*, making it superior to natural Coenzyme Q_{10} for treatment of CNS diseases with presumed mitochondrial dysfunction.

There are several secondary effects of idebenone described in the literature, which may be useful from the standpoint of the presumed pathophysiology of PP-MS:

3) Animal studies have documented neuroprotective properties of idebenone *in-vitro* in different models of excitotoxicity (by NMDA and kainite-agonists) *(Miyamoto and Coyle 1990, Bruno, Battaglia et al. 1994)*.
4) Idebenone induces nerve growth factor expression in animals *(Nitta, Murakami et al. 1994)*, which represented the basis for its presumed neuroprotective effect in Alzheimer's disease (AD) *(Gutzmann and Hadler 1998, Gutzmann, Kuhl et al. 2002)*. However, this beneficial effect on AD is only very mild and perhaps not highly clinically relevant *(Thal, Grundman et al. 2003)*.
5) Idebenone has potential CNS anti-inflammatory activity, as it inhibits metabolism of arachidonic acid by cyclooxygenase and lipoxygenase *(Civenni, Bezzi et al. 1999)*.
6) Idebenone may substitute for Coenzyme Q_{10} in non-mitochondrial locations such as in lysosomes, peroxisomes and plasma membranes, protecting these organelles from ROS-associated damage *(Geromel, Darin et al. 2002)*

Due to its effect as a scavenger of oxygen radicals and facilitating effect on ETC, idebenone has been used extensively with reported success in patients with mitochondrial diseases *(Mashima, Hiida et al. 1992, Ikejiri, Mori et al. 1996, Napolitano, Salvetti et al. 2000, Lerman-Sagie, Rustin et al. 2001, Geromel, Darin et al. 2002)*, although the desired prospective, double blind clinical trials in these patients have not been performed.

Perhaps the best documented and clinically meaningful example of sustained therapeutic benefit of idebenone in neurodegenerative disease is represented by Friedreich's ataxia (FRDA). FRDA is the most common hereditary ataxia inherited as an autosomal recessive GAA expansion in the first intron of the frataxin gene. Frataxin is a nuclear encoded protein, which is exported to the mitochondria. Frataxin plays an important role in the assembly of mitochondrial FE/S clusters that are key components of the ETC. Its decreased expression therefore leads to reduced activity of the ETC, mitochondrial damage with subsequent increased formation of reactive oxygen species (ROS). It was demonstrated that FRDA have reduced ATP biosynthesis, down to 30% of normal. (Lodi 1999). The reduced activity of the ETC in combination with secondary oxidative damage is believed to underlie the development of neurological disability and hypertrophic cardiomyopathy and diabetes, which are characteristic clinical presentations of this disease. Idebenone has been studied extensively in FRDA *(Schols, Vorgerd et al. 2001, Artuch, Aracil et al. 2002, Rustin, Rotig et al. 2002, Buyse, Mertens et al. 2003, Mariotti, Solari et al. 2003, Artuch, Aracil et al. 2004, Rustin, Bonnet et al. 2004, Di Prospero, Baker et al. 2007, Pineda, Arpa et al. 2008)*, including very successful studies performed at intramural NIH by the Neurogenetics Branch research group under the leadership of Dr. Kenneth Fischbeck (Di Prospero, Baker et al. 2007) in collaboration with Santhera. This study demonstrated that intermediate to high (10-50mg/kg) doses of idebenone were effective in slowing the progression of disability in FA patients as compared to low dose

idebenone (4-8mg/kg) and placebo. Because previous trials using lower doses of idebenone in FRDA demonstrated a positive effect on cardiac function but not on neurological function *(Mariotti, Solari et al. 2003)*, it is likely that higher doses of idebenone are necessary for penetration into the CNS.

In conclusion, the three major effects of idebenone (facilitating ETC mitochondrial function, antioxidant/scavenger of ROS and potentially also anti-inflammatory) make it an excellent candidate agent for the treatment of PP-MS based on the neurodegenerative hypothesis described above. Additionally, idebenone is an oral therapy with extensive safety and tolerability data.

4.7 Rationale for current study design

The clinical experience with use of antioxidants in MS is very limited: although a few trials of antioxidants in MS have been reported *(Jensen and Clausen 1986, Spitsin, Hooper et al. 2001, Yadav, Marracci et al. 2005)*, all have been small studies of short duration and offered only very limited insight on clinical efficacy *(Spitsin, Hooper et al. 2001)*.

Based on this background information, we propose to use idebenone in a proof-of-principle placebo-controlled cross-over Phase I/II clinical trial for PP-MS (Figure 1). Because there are no other therapeutic options for PP-MS, a placebo arm is both ethically justifiable and important to ensure an unbiased evaluation of MRI, clinical and immunological outcome measures. 1:1 randomization between active treatment and placebo will optimize statistical power for detecting differences in the outcome measures.

4.7.1 Figure 1

Idebenone in PP-MS clinical trial design

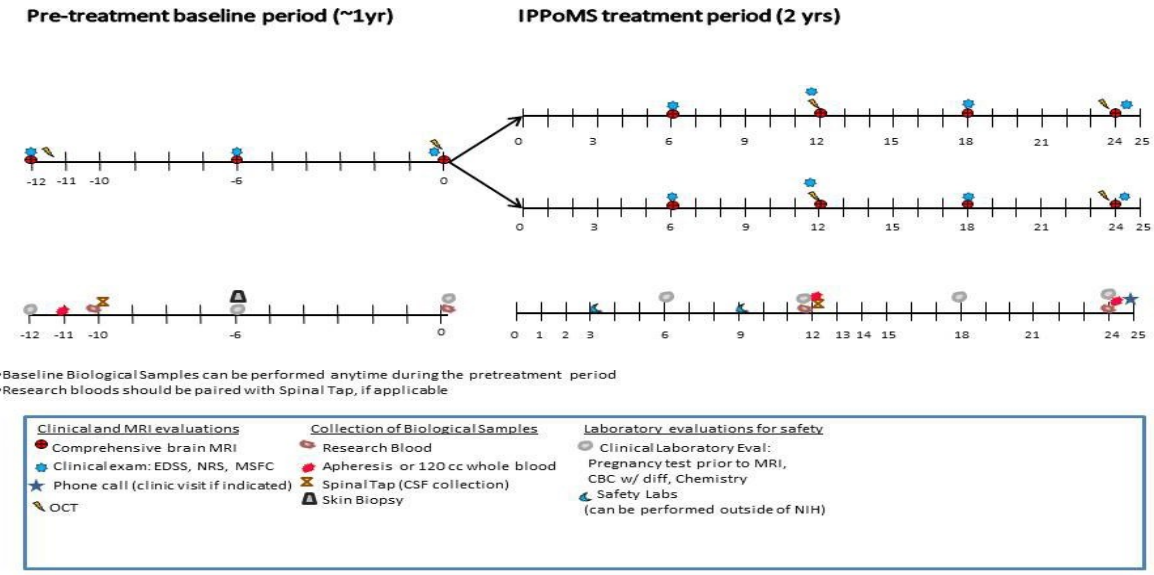

Figure 1: At least one year of pre-treatment baseline will be followed by 1:1 randomization to placebo and idebenone

750mg tid for 2 years. All outcome measures will be collected every 6-12 months as indicated.

There has not been a single successful therapeutic trial in PP-MS thus far and it has become obvious that outcome measures widely used in RR-MS trials are not suitable for PP-MS cohorts. Specifically, reliance on CEL as an outcome measure that allowed rapid screening of promising therapeutic agents in phase II trials of RR-MS patients is not possible in PP-MS, because these patients have a paucity of CEL and the frequency of CEL does not correlate with the development of clinical disability. However, current measurements of clinical disability are too insensitive to detect disease progression in individual PP-MS patients within 2-3 year time frame. As a consequence, promising agents for PP-MS have been tested so far in large, multi-center phase II/III trials, which are prohibitively expensive. Therefore, there is a great need to develop more sensitive measures of CNS tissue destruction that could be utilized as outcomes for smaller phase II trials in PP-MS. Currently the only measure that may theoretically fulfill this need is the individualized rate of development of brain atrophy as measured by SIENA methodology. However, it is highly probable that several newer measures of CNS tissue destruction, such as a decrease in the NAA/Cr ratio measured by MRS or quantitative T1 relaxation time, may be more sensitive than brain atrophy. The reason for this is that irreversible neuronal dysfunction may occur before the development of brain atrophy and that reactive gliosis, which is evident in the pathology of PP-MS, may to a large extent compensate volumetrically for the tissue loss associated with demyelination and neuronal drop-out. However, there are currently no available longitudinal measurements of these biomarkers to allow sample size estimates.

The possible solutions for this problem are twofold: We could perform a natural history study on PP-MS patients, collect longitudinal data and based on their analysis, design a new therapeutic trial of idebenone in the PP-MS population. However, this approach would pose significant delay for the therapeutic part of the trial and would also complicate recruitment efforts: even though none of the current disease modifying therapies (DMT) used in MS proved their efficacy in PP-MS, the relentless progression of neurological disability drives many PP-MS patients and their physicians to try unproved therapies. The second solution is to collect longitudinal data on PP-MS patients just before randomization to the treatment phase of the protocol. There are several advantages to this approach:

1) Because the longitudinal baseline (pre-randomization) data can be analyzed while patients proceed to the treatment phase, the administration of treatment does not have to be delayed until all patients complete pre-treatment baseline.
2) The NDU "natural history protocol" 09-N-0032, where patients with suspected MS undergo diagnostic work-up, explores the feasibility and utility of the proposed outcome measures. Hence, patients evaluated under this protocol with a final diagnosis of PP-MS can easily proceed to the therapeutic protocol, if so desired, and the data collected at NIB during the diagnostic work-up can be utilized as baseline (pre-randomization) data for the current therapeutic protocol. Historically, the baseline data have also been collected under NIB protocol 89-N-0045.
3) Finally, evidence indicates that the rate of CNS tissue destruction differs significantly among individual PP-MS patients, but remains intra-individually relatively stable (i.e. linear) during a 3-5 year follow-up (Ingle, Stevenson et al. 2003). Therefore, collecting 1 year of pre-treatment data on all patients in the therapeutic trial will allow us to calculate individualized rates of CNS tissue destruction and assess the therapeutic effect

of idebenone in relationship to these individualized rates of CNS tissue destruction. This is expected to increase the power of the trial to detect therapeutic effect (see below) without the need to stratify randomization of patients based on the rate of CNS tissue destruction, which is not feasible from the practical standpoint.

Based on this background, we propose to use an adaptive trial design: We will employ a pre-treatment baseline period of at least 12 months, where MRI, clinical and biomarker measurements will be collected in all patients for dual purpose:

1) To obtain longitudinal quantitative MRI, clinical and electrophysiological data in untreated PP-MS patients before randomization that will be utilized for the selection of the most sensitive primary outcome measure. This will be done on the first 30 patients and subsequent analysis will be used for selection of the most sensitive primary outcome measure and for adjusting sample size calculation (see sample size calculation, Section 11) if the primary outcome measure is different than brain atrophy measured by SIENA methodology and
2) To obtain patient-specific pre-randomization baseline for all collected outcome measures, which is expected to increase the statistical power of randomized trials with continuous outcome measures *(Murray, Barer et al. 2005, Young, Lees et al. 2005, Frost, Kenward et al. 2008)*. This is because previous longitudinal studies in PP-MS demonstrated that although there is extensive inter-individual variability in the rate of CNS tissue destruction, intra-individually, these rates are relatively stable within 3-5 year follow-up periods *(Ingle, Stevenson et al. 2002, Ingle, Stevenson et al. 2003, Stevenson, Ingle et al. 2004)*. In other words: the longitudinal data for the exact MRI, clinical and electrophysiological biomarkers of CNS tissue destruction and clinical disability that we propose to collect in this trial are not available. However, based on published longitudinal studies using analogous, but presumably less sensitive biomarkers of CNS tissue destruction (e.g. ventricular atrophy, cross-sectional cervical spinal cord atrophy collected at 1.5T MRI etc *(Ingle, Stevenson et al. 2003)*) we make two assumptions (Figure 2A): 1. CNS tissue destruction develops in a linear manner within a 3-5 year time-frame in the majority of PP-MS patients and 2. The slopes of the linear development of CNS tissue destruction differ among individual patients. Based on these two assumptions, our trial design will allow adjustment for the individualized rates of development of CNS tissue destruction (Figure 2B), which is expected to increase our power to detect treatment relevant differences between placebo and active therapy groups *(Murray, Barer et al. 2005, Young, Lees et al. 2005, Frost, Kenward et al. 2008)*.

The details of analyses of pre-randomization data on the first 30 subjects and the methods for selection of the most sensitive outcome measure are described in detail in Section 11, under Statistical Analyses.

Both active drug and placebo will be supplied by Santhera Pharmaceuticals.

We will use a 2250 mg/day dose (5x150mg tablets three times per day). This dose was well tolerated in Phase I trials in adult patients (Bodmer, Vankan et al. 2009) and ensures that each treated patient will receive 10-50mg/kg of idebenone per day, which represents the estimated dose required for CNS efficacy (Di Prospero, Baker et al. 2007).

Figure 2
Efficacy measures adjusted for individualized rates of development of CNS tissue destruction in PP-MS

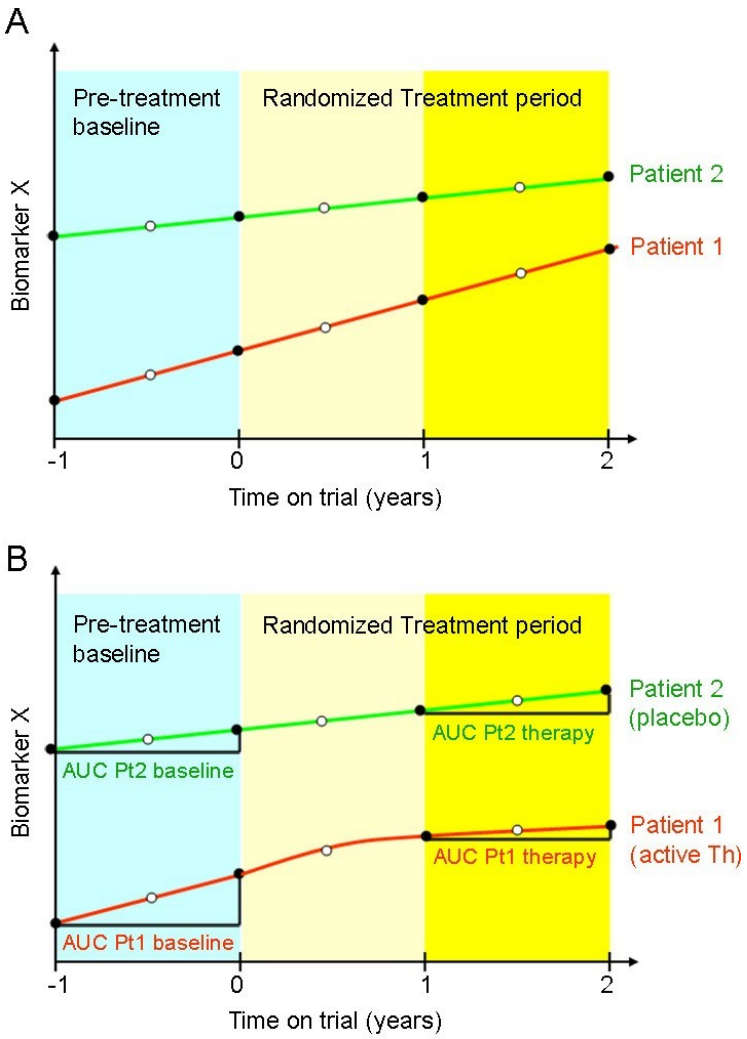

Figure 2:
A/ Current trial is based on three assumptions, which are supported by the literature (Ingle, Stevenson et al. 2003):

1. The slopes of CNS tissue destruction are linear for the majority of PP-MS patients. Therefore, the collection of 2-3 time-points for each biomarker during the baseline period will allow estimation of the individual slopes of CNS tissue destruction
2. The slopes of CNS tissue destruction differ among individual PP-MS patients
3. The cross-sectional data (i.e. single, initial measurement of the biomarker) do not predict the slope/rate of CNS tissue destruction

B/ Current trial and proposed analyses use the assumptions indicated above in order to increase the statistical power: for each patient, the area under curve (AUC) will be calculated for those biomarkers measured every 6 months and the AUC during the baseline period will be compared to the AUC during the second year of treatment in order to calculate the difference between these two measures. These individualized differences will be then compared on a group level between active treatment and placebo arms. For biomarkers collected every 12 months, the average of 2 baseline time-points (year -1 and 0) will be compared to the average of 2 therapy time-points (year 1 and 2) in an analogous manner.

Because this is a pilot study testing a novel mechanism of action (i.e. neuroprotection) in PP-MS with a very limited patient cohort, we need to optimize the trial design and select a patient population that is most likely to benefit from neuroprotective therapy in PP-MS. Specifically, we need to employ a patient population in which neuroprotection and repair are still feasible. Epidemiological data indicate that the major determinant of relentless progression of disability is a patient's age, and not necessarily disease duration *(Confavreux and Vukusic 2006)*. This may be due to the fact that natural repair mechanisms, including CNS plasticity and remyelination, decrease with aging *(Crutcher 2002, Confavreux and Vukusic 2006)*. It is likely that these natural

repair mechanisms are necessary for achieving effective neuroprotection. Furthermore, the aging process is characterized by decreased ECT function and accumulation of mitochondrial DNA mutations *(Lenaz, Bovina et al. 2002)*, which may complicate the differentiation between PP-MS-associated and aging-related mitochondrial dysfunction. The implementation of an upper age limit will eliminate these confounding factors. Because PP-MS is usually diagnosed in the early/late forties, we will limit the age of enrollment in this trial to 65. Setting an age limit will minimize the contribution of aging to the development of CNS atrophy and will ensure that aging will not limit CNS repair mechanisms. In contrast, we will not limit the disease duration. Because the most important outcome measures are neuro-imaging measures and those clinical/functional measures that are not necessarily skewed toward ambulation, we will include patients with moderate disability, up to EDSS 7.0 (i.e. patients who can ambulate with bilateral assistance). We will exclude non-ambulatory patients because of difficulties they would experience with prolonged MRIs, which are necessary for this protocol.

As such, the trial design is Phase I/II, double-blind, placebo controlled, baseline versus treatment with 2 parallel study groups of idebenone versus placebo (Figure 1).

Because of the paucity of suitable outcome measures for Phase II neuroprotective trials in MS, we will use/develop and validate several novel outcome measures in clinical, neuroimaging and immunological categories.

5. STUDY OBJECTIVES OR HYPOTHESES

5.1 Hypothesis

We hypothesize that idebenone, through its combined effect on facilitation of mitochondrial metabolism and limitation of oxygen radical-induced CNS damage, will inhibit CNS tissue destruction in PP-MS patients.

5.2 Goals of the study

The primary goals are:

1. To determine the safety of long-term (24 months) idebenone therapy at 2250 mg/day in patients with PP-MS.
2. To determine the efficacy of idebenone versus placebo in inhibiting individualized rates of CNS tissue destruction as measured by clinical biomarkers and quantitative imaging biomarker of brain atrophy (i.e. ventricular volume)

The secondary goals are:

1. To investigate the mechanism of action of idebenone in PP-MS.
2. To determine/define biomarkers of mitochondrial dysfunction and oxidative damage in PP-MS patients.
3. To define biomarkers indicative of therapeutic effect of idebenone on mitochondrial dysfunction and on limiting oxidative damage in PP-MS patients.
4. To collect longitudinal data in the placebo arm that will allow us to evaluate whether the assumptions on which we based our primary analysis (i.e. that the CNS tissue destruction is intra-individually linear, but inter-individually different within 3 year time period) are

correct or not. This will allow us to calculate more precise sample size/power calculations for future neuroprotective trials in PP-MS.

6. SUBJECTS

6.1 Study population

The study population will consist of 66 patients (33 per arm) with clinically definite PP-MS; age 18-65 (inclusive) with disability ranging from none to moderately severe (EDSS 1-7, inclusive). We will exclude children, because a diagnosis of PP-MS is virtually nonexistent in children, and we will limit the age of the participants up to 65, because of evidence that remyelination and repair strategies may be ineffective in older patients *(Crutcher 2002, Confavreux and Vukusic 2006)*.

Interested patients (i.e. those who respond to the advertisement or are referred by an outside physician) will be interviewed over the phone by one of the investigators and will be asked to fill out the standard NIB questionnaire (Appendix G, page 71) utilized also by the NIB natural history protocols 09-N-0032, and 89-N-0045. Patients will be informed that the information collected in the questionnaire is necessary for us to determine their eligibility to enter the protocol and that collection and review of these personal data will be performed under NIH/NINDS principles for patient confidentiality. Verbal consent for collection and review of the personal data will be obtained from interested patients by study investigators. The following standard language for obtaining verbal phone consent will be used:

> "Thank you for calling the Neuroimmunology Branch. I am (name). The Neuroimmunology Branch studies multiple sclerosis, along with other diseases of the central nervous system. If you are interested in participating in one of our studies, I will send you our screening questionnaire. This questionnaire will expedite the screening process to see if you qualify for any of our current or future studies. The questionnaire takes about 10 minutes to complete. If you appear to be eligible for a study, you will be invited to come to the NIH for a clinical visit and possible enrollment in one of our studies.
> The questionnaire asks you to provide confidential information related to your health. You must understand the risks and possible benefits of completing this questionnaire and then you can decide whether to continue.
> First, the benefits. There is no direct medical benefit to you from completing this questionnaire, but we should be able to determine whether it is worth your time to come in for a clinical visit and possible enrollment in a study.
> Now the risks. Some of the information requested in the questionnaire is very personal. We will keep it as confidential as possible, using secure computers and locked files.
> Your participation in this screening questionnaire is completely voluntary. You do not have to answer every question, but if you skip too many questions, we may not be able to determine if you

are eligible for any NIB studies. There is no payment for completing this questionnaire. If you have questions or concerns about this process, you may contact our clinical staff at 301-496-0064. Do you agree to participate?"

The date and time the consent is obtained will be documented and witnessed, and this will be included in the research record.

6.2 Inclusion criteria

1. PP-MS as determined by the 2005 modification of McDonald's diagnostic criteria (see appendix E, page 64) *(Polman, Reingold et al. 2005)*
2. Age from 18-65 years (inclusive)
3. EDSS measure of neurological disability from 1 (no disability, clinical signs only) to 7 (ambulatory with bilateral support) *(Kurtzke 1983)* at the time of first screening visit to NIH.
4. Able to provide informed consent
5. Willing to participate in all aspects of trial design and follow-up
6. If able to become pregnant or to father a child, agreeing to commit to the use of a reliable/accepted method of birth control (i.e. hormonal contraception (birth control pills, injected hormones, vaginal ring), intrauterine device, barrier methods with spermicide (diaphragm with spermicide, condom with spermicide) or surgical sterilization (hysterectomy, tubal ligation, or vasectomy) for the duration of treatment arm of the study
7. Not receiving any immunomodulatory/immunosuppressive therapies for a period of at least 3 months before enrollment in the study
8. No exposure to idebenone, coenzyme-Q_{10} or other dietary supplements (such as antioxidants, mitochondrial-function promoting supplements or vitamins in excess of 3 times recommended daily doses) for a period of at least 1 month before enrollment in the study

A single patient (NIB 334) has been granted an amendment to inclusion criteria #2. NIB 334 meets all remaining inclusion and none of the exclusion criteria for the study. This patient has no comorbidities. If this patient is completes the baseline and is dosed with idebenone/placebo, he will be analyzed the same as other patients. The FDA was consulted, and expressed no objections to this plan.

6.3 Exclusion criteria

1. Alternative diagnoses that can explain neurological disability and MRI findings
2. Clinically significant medical disorders that, in the judgment of the investigators could cause CNS tissue damage or limit its repair, or might expose the patient to undue risk of harm or prevent the patient from completing the study
3. History of hypersensitivity reaction to idebenone or coenzyme-Q_{10}
4. Pregnant or lactating women. All women of child-bearing potential must have a negative pregnancy test prior to the medication phase of the study.
5. Abnormal screening/baseline blood tests exceeding any of the limits defined below:

i. Serum alanine transaminase or aspartate transaminase levels greater than 3 times the upper limit of normal values
ii. Total white blood cell count < 3,000/mm^3
iii. Platelet count < 85,000/mm^3
iv. Serum creatinine level > 2.0 mg/dl or eGFR (glomerular filtration rate) <30
v. Positive pregnancy test

6. Patients who are receiving any immunosuppressive therapies (including cytostatic agents) due to the concern that these drugs may contribute to neurodegeneration or limit CNS repair

7. STUDY DESIGN AND METHODS

7.1 Study overview

This is a Phase I/II, double-blind, placebo controlled, baseline versus treatment with 2 parallel study groups (Figure 1) and an adaptive trial design.

Based on current sample size estimates we expect to screen up to 85 PP-MS to yield at least 66 patients that will finish the treatment phase of the study. These patients will be randomized 1:1 to receive either active therapy (idebenone 750mg po tid) or matched placebo. The treatment phase of the trial will be preceded by a 1 year pre-treatment baseline period, which will serve a dual purpose: 1. To collect individualized data on biomarkers of CNS tissue damage and 2. To use these longitudinal data for the selection of the primary outcome measure and for more precise sample size estimates.

7.2 Recruitment

This protocol will be advertised on the NIH website and through patient support groups such as the National MS Society (NMSS). Active recruitment will include a letter to neurologists in the greater Washington DC area and to MS specialists in the states of Virginia, West Virginia, Maryland, Delaware, New Jersey and Pennsylvania. We have contracted the recruitment services of the North American Research Committee on Multiple Sclerosis (NARCOMS). The NARCOMS registry is a database of MS patient volunteers who are interested in participating in research. NARCOMS collects volunteer data, and then will match the volunteers to applicable studies. Volunteers are then mailed information about the studies they match, and the participant is able to contact the studies they are interested in. Finally, eligible patients will also be recruited from NIB natural history protocols (09-N-0032 and 89-N-0045). Because this natural history protocol collects identical clinical, MRI and paraclinical data as the present protocol, we will use data already collected under the natural history protocol in order to fulfill the requirements of the pre-treatment baseline. This will allow eligible PP-MS patients to proceed to the randomization and treatment phase of the current protocol without unnecessary delay.

Patient advertisement (for NIH website and for NMSS bulletin) and the letter to the neurologists are provided in Appendix F.

7.3 Screening methods

Patients who contact the study either through physician or self referral will be screened initially by phone. Interested patients may be requested to complete the NIB MS questionnaire (Appendix G) and to provide pertinent medical records (including MRI of the brain/spinal cord). The blank questionnaire may be sent to the potential patient by mail, fax, or email. The completed questionnaire and medical records are then mailed or faxed to the protocol research contact. Upon receipt of the records and imaging studies, the patient will be contacted to confirm the receipt of the requested information and, provided that review of the documentation does not identify any exclusion criteria, the patient will be invited to participate in the study. Interested patients will be scheduled for outpatient admission to the Clinical Center.

Subjects who sign the informed consent but are excluded later based on abnormal laboratory findings will be defined as screen failures and counted toward patient accrual. When 30 subjects complete the pre-treatment baseline, we will perform an interim analysis for more precise sample size calculations (See Sample size calculation, section 11) and for selection of the most sensitive primary outcome measure. This analysis will not require unblinding, and will not affect final statistical analysis. Instead, it will help us to perform more precise power calculations based on longitudinal data collected utilizing neuroimaging biomarkers specific for this trial. We expect that this interim analysis will allow us to increase the power and/or decrease the sample size, based on assumptions specified under Section 11 and outlined in Figure 2.

To allow for approximately 20% screening failures, the accrual ceiling (based on current estimates of sample size) will be set at 80 patients.

7.4 Study design

All eligible patients will undergo combined neurological, neuroimaging and research biomarker/immunological evaluations as outlined in Fig. 1 for the baseline period. The complete baseline evaluation will require approximately 4 outpatient visits in approximately 1 year. Each outpatient visit will last 3-5 hours.

Patients who complete the baseline period will be randomized to active treatment or placebo by block stratification (by block size of 2) using a single condition: 1. Age (age <50 and age ≥50). Because epidemiological data indicate that age is a major determinant of the efficiency of CNS repair *(Crutcher 2002, Confavreux and Vukusic 2006)*, this randomization strategy will ensure that both placebo and active treatment groups are comparable in this respect. The majority of patients are diagnosed with PP-MS around age 40. Furthermore, using block size of 2 will assure balanced distribution of the first 30 patients into placebo and active treatment groups (i.e. 15 patients per group). Randomization will be performed by the NIH pharmacy. The NIH pharmacy will maintain the study code key and release it to the investigators only after completion of the trial and finalization of the database. The NIH pharmacy may release the study code to the DSMB, if requested.

After randomization, patients will be followed by combined neurological, neuroimaging and research biomarker/immunological evaluations as outlined in Fig. 1 for an additional 24 months.

The time commitment will include at least 6 outpatient visits in the 2 year period. Each outpatient visit will last 2-5 hours.

According to the negotiated CTA, Santhera Inc. will supply a sufficient amount of idebenone for completion of the proposed trial (i.e. 2 year dosing for 40 patients). There is no negotiated provision for Santhera to continue to provide drug on a compassionate basis for any of the patients after completion of the trial.

7.5 Study procedures

7.5.1 Study visits

Each study visit (Figure 1) and MRIs should occur as indicated. These time points are approximated. To accommodate for patient scheduling needs or clinical necessity, study visits will be accepted within a +/- 4 week window of the timepoints noted. Biological samples (CSF, whole blood, apheresis sample) should be collected within 4 weeks of the MRI examination as indicated in Figure 1. Blood samples at baseline and 1 year of treatment will be collected concomitantly with CSF samples.

7.5.2 Clinical and functional evaluations:

to be performed every 6 months

1. Comprehensive neurological evaluation
2. Expanded Disability Status Scale (EDSS *(Kurtzke 1983)*)
3. Scripps Neurological Rating Scale (NRS *(Sharrack and Hughes 1996)*)
4. MS Functional Composite Scale (MSFC *(Cutter, Baier et al. 1999)*, which consists of 3 functional tests:
    a. Paced Auditory Single Digit Addition Test (PASAT) – measure of cognitive skills
    b. Timed 25 foot walk – measure of ambulation
    c. 9-hole peg test – measure of fine finger motor movements
5. Symbol Digit Modality Test *(Sepulcre, Vanotti et al. 2006)*
6. Extensive evaluation of strength, balance and gait within the context of a physical therapy (PT) evaluation may be performed if the subject is not too disabled to participate in these evaluations safely and reliably. This optional evaluation will be conducted in the Biomechanics Laboratory of the Rehabilitation Medicine Department, NIH, CC. It will include, but may not be limited to, the following:
    a. Evaluation of strength and tone
    b. Evaluation of gait
    c. Balance assessment

    The assessment of strength and spasticity may require the use of surface EMG.

7.5.3 Neuroimaging evaluation:

MRI imaging will consist of combined MRI of the brain and upper cervical spinal cord, which will be performed every 6 months. This MRI will focus on quantitative and volumetric analyses of brain structure and tissue integrity. Inflammatory activity is less prominent in PP-MS as compared to RR-

MS and consequently, the vast majority of PP-MS patients do not have evidence of gross blood-brain barrier (BBB) disruption as measured by contrast-enhancing lesions (CEL). This is confirmed in our experience in this trial thus far, where true CEL are extremely rare at baseline and their incidence is not increased during the treatment phase. Therefore, we will administer contrast only at the first NIH MRI to identify those patients who may have very rare form of inflammatory PP-MS. Clinical judgment will determine if Gd is administered during the remaining 3T brain MRI scans. The total scan time without Gd administration is approximately 60 minutes. With Gd, the scan time increases to 90 minutes. Because more disabled patients have difficulties with long scans and it is paramount for the integrity of quantitative MRI data to avoid patient movement, the elimination of contrast administration from subsequent scans will improve tolerability of MRI procedure and improve MRI data quality without compromising the safety of patients.

7.5.4 Optical coherence tomography (OCT)

To be performed every 12 months

OCT is a new noninvasive high-resolution method that measures the retinal nerve fiber layer (RNFL) thickness. It works by measuring the echo time delay and intensity of back-reflection of light from different structures in the eye. Recent studies have shown that OCT can detect RNFL thinning, possibly due to axon degeneration, within the retinas of patients with MS, regardless of a clinical history of optic neuritis (Kallenbach and Frederiksen 2007). Moreover, RNFL thickness appears associated with global brain atrophy, (manifested by increasing CSF volume) (Gordon-Lipkin, Chodkowski et al. 2007). As discussed, reliable methods of measurement of neurodegeneration in MS are lacking. While a more thorough characterization is needed, evidence to date suggests that OCT may be developed as a novel measure of neuronal/axonal destruction reflective of neurodegeneration in MS with both diagnostic and prognostic potential *(Gordon-Lipkin, Chodkowski et al. 2007, Kallenbach and Frederiksen 2007)*.

7.5.5 Transcranial magnetic stimulation (TMS) and Central motor conduction time (CMCT) calculation

May be performed for clinical care.

Neurophysiological testing, can assess the intactness of conduction through the long tracts, such as the corticospinal tract (CST) *(Ravnborg 1996)*. Because CST is invariably affected in PP-MS, the use of motor evoked potentials (MEP) may be performed for clinical care. TMS is a non-invasive technique for evaluating the function of central motor pathways. Single pulse TMS is used to determine the motor evoked potential (MEP), the response generated by excitation of cortical neurons and recorded at the target muscle, and is used to calculate the central motor conduction time (CMCT). In MS patients, CNS dysfunction manifests itself in the form of slowed conduction through demyelinated portions of the corticospinal tracts or more severe disruption of conduction as a result of axonal loss or severe demyelination. This results in a prolongation of CMCT or dispersion of the MEP response such as in a conduction block with resultant decrease in MEP amplitude *(Hess, Mills et al. 1987, Schriefer, Hess et al. 1989)*. In progressive MS patients, CMCT has been shown to correlate with the presence of new spinal cord lesions on MRI and changes in the leg CMCT *(Kidd, Thompson et al. 1998)*. There is other evidence that suggests that progressive MS patients have greater prolongation of the CMCT compared to relapsing-remitting MS, irrespective of MRI lesion load, suggesting that progressive MS has more perturbations of the corticospinal tracts than are radiologically discernible *(Humm, Z'Graggen et al. 2004)*.

7.5.6 Immunological and laboratory evaluation

The immunological and laboratory evaluation will include:

1. Diagnostic/clinical blood-work (clinical care/safety): Baseline labs on untreated patients may be collected under this protocol, or our natural history protocols (09-N-0032 or 89-N-0045). CBC, Chemistry panel including liver function tests will be performed every 3 months for the first year of treatment and every 6 months for the second year of treatment as part of the safety measures. Laboratory evaluations that are performed at times when no NIH MRI/clinical visit is scheduled can be performed outside of NIH with results (including normal values) communicated to NIH investigators. Urine analysis (UA) will be performed every 6 months. Pregnancy tests (for females of child-bearing potential) will be collected up to 24h preceding every MRI exam. All safety laboratory evaluations are represented in the clinical trial scheme on Figure 1.
2. Research Blood (up to 60 cc total):Research blood will be obtained approximately every 12 months (2 baseline and 2 treatment samples); this will be aliquoted and stored or used at the time of collection to meet the Biological/Immunological outcomes stated in section 10.
3. CBC: Additional CBC may be performed in coordination with the research blood if a CBC is not already indicated at these timepoints. This information will be collected solely for research purposes.
4. Lumbar puncture (research): Every patient will undergo a lumbar puncture twice during protocol duration: once at baseline (can be diagnostic LP from which 15-20cc of CSF has been obtained for research for total of 25cc of CSF collected in total) and once after 1 year of therapy (month 12). If the participant has undergone lumbar puncture at any time during their participation in the screening protocol and an adequate sample is already available, this may replace the baseline LP at the discretion of the Principle Investigator. From 15-20cc of research specimen, immune cells will be isolated and expanded and the CSF supernatant will be aliquoted and stored. Lumbar puncture procedure last from 30 minutes to 2 hours. The lumbar puncture will usually be done on an inpatient or day hospital floor of the Clinical Center. The procedure may be performed under fluoroscopic guidance by a credentialed neuroradiologist in Diagnostic Radiology, if there is a patient medical or scheduling need to do so. This involves a small amount of ionizing radiation (0.023 rem per LP). This is substantially less than the limits imposed by the guidelines of the NIH Radiation Safety Committee (5.0 rem per year for adults).

5. Pharmacokinetic (PK) studies (research): Random sampling PK studies may be performed from the CSF twice during the duration of the protocol; at the time of LP. The first sample may be collected at baseline, prior to administration of study medication. The second sample may be collected at month 12 (+/- 2 weeks) of therapy, between 1 and 4 hours after idebenone intake (time selected randomly and documented in the research database). For the analysis of free and total idebenone and its metabolites free and total QS-10, total QS-6 and total QS-4, 8 ml CSF will be taken into two different tubes: 1. For the measurement of total idebenone and its metabolites total QS-10, total QS-6 and total QS-4: 0.5ml of CSF will be collected. For the measurement of free idebenone and its metabolite free QS-10 (i.e. active substances): 0.5ml of CSF will be collected. Samples will be put on ice immediately and centrifuged at 4°C at 1500 g for 10 minutes within 30 minutes after sampling. The cell-free aliquots will be separated and stored separately in polypropylene tubes with a minimum of 0.5ml of CSF per tube. Samples will be stored between -70 and -80°C. The CSF will be collected for possible future PK studies

to be performed by Santhera Pharmaceuticals upon completion of the collection of all trial samples, using a validated LC-MS/MS method (Inovalab, Reinach, Switzerland)

6. Lymphocytapheresis (research): collecting between 2-4x10^9 peripheral blood mononuclear cells PBMC, will be performed 3 times during trial: once during pre-treatment baseline and after 1 (month 12) and 2 (month 24) years of treatment. This procedure is performed solely for research purposes. If the participant has undergone lymphocytapheresis at any time during their participation in the screening protocol and an adequate sample is already available, this may replace the baseline lymphocytapheresis at the discretion of the Principle Investigator. This procedure may last up to 2.5 hours. If the participant is unable to undergo lymphocytapheresis for any reason, 120 cc of whole blood in a heparinized syringe will be collected in its place. The collected mononuclear cells (up to 4x10^9) will be used for immunological studies.
7. Skin biopsy (research): the punch skin biopsy will be collected once during baseline period. Skin biopsy will be used for isolation, expansion and cryopreservation of fibroblasts for future studies. Specifically, the fibroblast will be transformed to induced pluripotent stem cells (iPS), which can then be differentiated into neurons and glial cells. The purpose of these future studies is to evaluate if neurons from PP-MS patients are more susceptible to oxidative damage than neurons from other forms of MS (RR-MS and SP-MS) and neurons derived from patients with other disorders (i.e. controls). These future studies will be performed only after sufficient number of control samples of fibroblasts are collected/banked under alternative NIB protocols.

7.5.7 Drug administration

We requested a new investigational new drug (IND) number from Food and Drug Administration (FDA) on 3/9/09. A copy of this protocol has been submitted to the FDA for review.

Idebenone (150mg tablets) or placebo will be administered orally as five tablets, three times per day with food. Patients will receive a 6 month supply of the study medication. Patients will record drug administration in a drug diary to monitor compliance. Remaining pills and bottles will be counted during clinic visits every 6 months to assess overall drug compliance.

Idebenone is a short-chain benzoquinone derivative of similar structure to ubiquinone (coenzyme Q_{10}). This compound was synthesized and developed initially by Takeda Chemical Industries, Ltd. (Osaka, Japan) and designated as CV-2619. The chemical name for idebenone is 6-(10-Hydroxydecyl)-2,3-dimethoxy-5-methyl-1,4-benzoquinone. Santhera Pharmaceuticals (Switzerland) Ltd, will supply the drug for this study as specified by a clinical trial agreement (Appendix H). Idebenone is formulated as film-coated 150 mg tablets. For list of inactive ingredients see section 4.5.4.

Idebenone with a certificate documenting analytical results, release of the product for the clinical study and shelf life will be provided to the NINDS by Santhera Pharmaceuticals (Switzerland) Ltd. Idebenone tablets and matching placebo are supplied in high density polyethylene (HDPE) bottles, stored at room temperature (15-25ºC) and must be protected from direct sunlight. Temperature excursions are permitted as follows: up to 30ºC for 12 months, up to 40ºC for 6 months.

7.5.8 Records

The NINDS/Clinical center record will be used for trial-related documentation. Specific trial-related pages will include:

1. Inclusion and exclusion criteria checklist
2. Documentation of the history and physical examination (using structured NIB progress note).
3. A copy of the written informed consent.
4. A record of all research tests, scores, and results.
5. Documentation of all clinical laboratory results.
6. Documentation of any concomitant medications taken by the patient.
7. A record of any and all adverse events experienced during the study.

7.5.9 Storage of data and samples

All collected samples, including serum, blood, CSF, expanded fibroblasts and peripheral blood mononuclear cells (PBMC) derived from aphereses, will be coded and stored in secured freezers on the NIH campus. All patients enrolled in this protocol will be assigned a sequential code and all biological samples collected for this patient will be labeled with patient's code, type of the sample, volume, number of cells (if indicated) and date of freezing.

The intent is for all samples to be analyzed in laboratories on the NIH campus. As new relevant methodologies are developed, however, there is a conceivable future interest to process samples off-site in a collaborating laboratory. Patients will be made aware of this possibility at the time of enrollment and will be asked to consent to potential off-site processing. In this event, IRB approval from NIH and from the collaborating institution will be obtained, and materials will be shipped in accordance with NIH and federal regulations.

7.6 Follow-up/termination procedures

7.6.10 Trial termination procedures

The individual participation in the trial will end with the last trial visit at month 24. There will be a telephone interview 1 month after completion of the trial to verify that there has been no worsening of the clinical symptoms. In case of serious adverse events ongoing at the last trial visit (month 24) **or** of SAEs newly reported during the telephone contact, the patient will be invited to undergo a full examination and assessment at the study site. Additionally, patients will be asked to report any serious adverse event that may occur after this last interview, if they perceive them as possibly related to the participation in this study. The trial will be officially terminated after all enrolled subjects complete the last scheduled visit (month 24) or withdraw from the trial. The trial may be terminated prematurely by the DSMB if there is a concern about safety of idebenone in PP-MS patients. Because no interim analysis requiring unblinding of patient allocation is planned, there will be no termination of the trial based on therapeutic futility.

As of this protocol amendment, data analysis has been completed and demonstrated that idebenone, while being safe and well-tolerated, had no significant efficacy on either primary or any secondary outcome measures, in comparison to placebo. Data and samples from this study will be transferred into protocol 09-N-0032 for continued analysis. Participants will be formally informed of the study results by a written letter (uploaded to PTMS).

All clinical data will be prospectively acquired and entered into the NIB research database. Similarly, all neuroimaging volumetric data will be transcribed into the NIB research database. All immunological and/or biomarker data will be logged and stored in a separate research database on the NINDS server. In order to limit inter-assay variability, for those biomarkers that can be assessed from cryopreserved biological samples, all time-points for individual research subjects will be run in parallel. All databases will be locked upon the last entry of data from the last patient who completes the trial.

7.6.11 Assessment of the efficacy of blinding

Efficacy of blinding will be assessed two times during the trial duration for research subjects and clinical evaluators: At month 6 and after completion of the trial. These evaluations will be administered in person. Similarly, efficacy of blinding for those investigators/data assessors who perform analysis of neuroimaging and immunological data will be assessed twice: at the beginning of their analysis and at the end. Because some of the data acquired during therapy time-points (especially biological/immunological markers) are likely to be influenced by treatment allocation, investigators performing immunological assays will have no access to clinical/MRI data and vice versa. The only person who will have access to all data simultaneously and who will monitor integrity and technical quality of performed analyses will be the PI. However, the PI will not serve as a clinical evaluator.

7.6.12 Release of allocation code

The allocation code will be provided to the investigators by the NIH pharmacy only after all the required analyses (i.e. all primary and secondary outcome measures) have been collected, research databases have been locked and assessment of blinding has been performed.

8. RISKS/DISCOMFORTS

8.1 Risks associated with Idebenone therapy

There is considerable clinical trial and post-marketing experience indicating that idebenone is well tolerated and has a good safety profile. The most relevant adverse reaction data is provided by a recent placebo-controlled study with 48 Friedreich's Ataxia patients below the age of 18 years. Due to the limited sample, frequencies can not be reliably calculated. The most commonly observed adverse reactions were gastrointestinal disorders. The following reactions were observed in more than one patient: headache, diarrhea, nausea and dyspepsia. The following reactions were not observed in more than one patient at the recommended doses: white blood cell count decrease,

disturbance in attention, angina pectoris, vomiting, reflux oesophagitis, musculoskeletal chest pain, myalgia, chromaturia, upper abdominal pain.

Clinical trials with idebenone have previously been performed in indications other than FRDA, predominantly in older patient populations (mainly in Alzheimer's dementia) not readily comparable with FRDA. Besides some of the reactions listed above, patients in these trials showed the following reactions uncommonly (between 1/1000 and 1/100): sleep disorders, nervousness, dizziness, changes in hepatic laboratory values and influenza-like symptoms. These reactions may be more likely in this elderly study population with CNS impairment and more concomitant medications.

Idebenone has not been administered (to our knowledge) to patients with presumed immune-mediated disorders and therefore the effect of idebenone on dysregulated immune responses in humans is currently unknown and difficult to predict. Because several functions of the immune system are dependent of the formation of ROS, a potent antioxidant may theoretically inhibit these functions. Among these are oxidative burst used by granulocytes and monocytes/macrophages to kill intracellular pathogens and granzyme A-, B- and K-mediated killing utilized by natural killer (NK) cells and some T cells. Granzyme-B mediated killing is only partially dependent on the formation of ROS, as it predominantly relies on activation of caspases. Because some of these immune functions (oxidative burst of monocytes/macrophages, including microglia and granzyme-B-mediated killing by cytotoxic T cells) are thought to contribute to CNS tissue damage in MS, theoretical inhibition of these functions by idebenone may have an overall beneficial effect in PP-MS patients.

Inhibition of oxidative burst utilized by granulocytes and monocytes/macrophages can theoretically lead to increased rates of infections; however, this was not observed in double-blinded placebo controlled randomized trials, including those that targeted elderly and disabled patients (e.g. AD), which are known to be more susceptible to infectious complications. Therefore, idebenone is considered to be a safe and well tolerated agent.

Idebenone at high doses (60-75 mg/kg/day or about 3600-4500 mg/day) may cause orange discoloration of urine in few patients. It is unclear if this will occur at the dose of 2250mg/day. The orange discoloration of urine is completely harmless and urine will be monitored every 6 months by urinalysis in order to ensure that hematuria or hemoglobinuria is not mistaken for the orange discoloration due to idebenone.

8.2 Risks of lymphocytapheresis

Adverse reactions associated with lymphocytapheresis include vasovagal syncope with needle insertion and rare hypotension secondary to volume depletion. Because of the controlled nature of these procedures hypotension is unlikely. Exclusion of patients with a history of cardiovascular disease further reduces the risk of this complication. The blood thinner used to prevent blood clots from apheresis can cause mild muscle cramps. If these side effects occur, we can slow down blood flow or use a different blood thinner. If the symptoms do not go away, the apheresis can be stopped. There may also be bruising at the site of needle insertion. Infection is a potential risk, but is unlikely due to the closed system and the maintenance of sterile technique. The Blood Bank has extensive experience with these procedures and has encountered no serious side effects.

8.3 Risks of MRI

People are at risk for injury from the MRI magnet if they have pacemakers or other implanted electrical devices, brain stimulators, dental implants, aneurysm clips (metal clips on the wall of a large artery), metallic prostheses (including metal pins and rods, heart valves, and cochlear implants), permanent eyeliner or tattoos, implanted delivery pump, or shrapnel fragments. Welders and metal workers are also at risk for injury because of possible small metal fragments in the eye, of which they may be unaware. All subjects will be screened for these conditions prior to the study, and if they have any, they will not receive an MRI scan.

Gadolinium is a contrast agent approved for use with MRI by the FDA. No serious side effects have been associated with its use. The effect of gadolinium on the developing fetus remains partly unknown. Animal studies have shown a delay in development but no developmental abnormalities. Consequently, women of childbearing potential will be entered into this study only if an effective means of birth control is in use. A pregnancy test will be done prior to beginning the study and monthly pregnancy tests will be done before MRIs are performed. The risks of an IV catheter include bleeding, infection, or inflammation of the skin and vein with pain and swelling. Symptoms from the contrast infusion are usually mild and may include coldness in the arm during the injection, a metallic taste, headache, and nausea. In an extremely small number of patients, more severe symptoms have been reported including shortness of breath, wheezing, hives, and lowering of blood pressure. Subjects should not receive gadolinium-based contrast agents if they have previously had an allergic reaction to them. Subjects will be asked about such allergic reactions before a contrast agent is administered. People with kidney disease are at risk for a serious reaction to gadolinium contrast called “nephrogenic systemic fibrosis” which has resulted in a very small number of deaths. If patients are older than 60 or have diabetes, kidney disease or liver disease, bloodwork to assess kidney function will be performed within 4 weeks before any MRI scan with gadolinium contrast. Patients may not receive gadolinium for a research MRI scan if kidney function is not normal. The long term effect of noise exposure from MRI is not known.

8.4 Risks of lumbar puncture

Adverse effects associated with lumbar punctures include brief pain or tingling paresthesias radiating down the lower extremity due to the needle brushing against a nerve. Should this occur, the needle can be repositioned. Mild lower back pain at the site of needle insertion following the procedure can occur; this can be managed with over the counter non-steroidal anti-inflammatory agents if needed. In approximately one third of patients, a post-dural puncture headache may develop and persist for a few days; in one in 50 to 200 lumbar punctures the post-dural puncture headache can last longer than 7 days. Generally this headache is not severe and resolves spontaneously within days - 2 weeks. Should the headache persist or be severe, a blood patch can be performed. An extremely rare complication of lumbar puncture includes temporary double vision related to abducens nerve palsy, and infection. Strict aseptic technique will be followed. Collecting additional 10-15 cc of CSF per procedure represents negligible risk (Evans, Armon et al. 2000). In humans the rate of CSF synthesis is approximately 21.5 cc/hour (Kimelberg 2004), or approximately 500cc/24hours, which represents roughly 4 times the total volume of CSF in an adult patients. Therefore, the volume of 20-30cc of CSF that would be collected for both diagnostic and research purposes will be replenished in its entirety within approximately 1-1.5 hours after collection.

Lumbar puncture may be done in the radiology department under fluoroscopic guidance for patient medical or scheduling needs. The total radiation exposure during the 2 procedures is 0.046 rem, which is well below the guideline of 5 rem per year allowed for research subjects by the NIH Radiation Safety Committee.

8.5 Risk of OCT

There are no known medical risks of optical coherence tomography.

8.6 Risk of electrophysiological studies

8.6.13 Risk of TMS

TMS is a safe procedure that has been used on thousands of people throughout the world, particularly the single-pulse TMS used in this study. Most people do not find the stimulation painful, but sometimes strong contractions of scalp muscles can cause discomfort or headache. Headaches usually go away promptly with nonprescription medication. The noise of the TMS magnet may damage hearing, therefore the subjects will be fitted with earplugs that must be worn during TMS. TMS can interfere with implanted medical devices and will not be done in people who have pacemakers, implanted pumps, or stimulators, such as cochlear implants or in people who have metal objects inside the eye or skull.

8.6.14 Risk of nerve conduction studies

The risks of the electrical stimulation using commercial isolated stimulators are low. Most subjects find electrical nerve shocks to be mildly uncomfortable; it is usually perceived as a brief stinging or tapping sensation. The intensities required for nerve conduction studies are usually well tolerated.

8.7 Risk of skin biopsy

Pain at the biopsy site is usually minimal; bleeding and infection are rare. The biopsy site usually heals with a very small, nearly unnoticeable scar, but may leave a raised scar or visible lump.

8.8 Risk Rehab Evaluation

The risk of physical injury in this series of noninvasive tests is minimal.

9. SUBJECT MONITORING

9.1 Parameters to be monitored

9.1.15 Expected Adverse Events

Animal studies predict a low human toxicity profile for idebenone. This is supported by extensive experience including phase I trials in normal human volunteers and phase II and III trials in patients with Alzheimer's disease, Friedreich's Ataxia, cerebrovascular accident (stroke), multi-infarct dementia, and other neurodegenerative diseases (e.g. Huntington's disease). The most frequently and consistently experienced adverse reactions reported across these trials have been headache, diarrhea, nausea and dyspepsia. Events (reported by ≥ 3% of patients) across double-blinded

placebo controlled randomized trials included abdominal pain (8.9%), diarrhea (6.6%), flu-like syndrome (5.5%), accidental injury (4.6%), depression (4.6%), upper respiratory tract infection (4.5%), headache (3.9%), back pain (3.7%), agitation (3.5%), urinary tract infection (3.2%), and dizziness (3.0%). The events occurred with similar frequency in patients receiving placebo and thus were not felt to be drug related. These events are typically mild to moderate in severity and reversible. A complete list of previous adverse events, which may also be expected in this trial, may be found in the Investigator's Brochure and is summarized in section 7 of that document. In addition, medical events typical for clinical course of PP-MS (i.e. typical neurological signs/symptoms that patient experienced during pre-treatment baseline and their worsening as would be expected from the natural history of PP-MS) can be regarded as expected events in the course of the current trial.

9.1.16 Monitoring of adverse events

The patient will be instructed to contact the investigator immediately should the patient manifest any sign or symptom perceived as serious during the period extending from performance of the first study procedure (e.g. drawing of a blood sample) up to and including 1 month after the last dose (telephone interview at month 25). After this period of time, the patient should report to the investigator only adverse events that are serious and perceived as possibly related to their participation in this study.

Additionally, the patient will be instructed to contact the investigator immediately if he/she believes that he/she has fathered/conceived a child. Testing would be performed to verify that the subject or subject's partner was pregnant. If the pregnancy test were positive, the patient would be instructed to immediately stop taking the study drug and his/her treatment assignment would be revealed to the investigators and the DSMB. The patient or partner would be counseled and followed closely during the pregnancy by the NIH research team and would implement any recommendations made by the DSMB.

Patients will be physically examined by the investigator approximately every 6 months for the study duration. Extensive laboratory monitoring of the following will occur every 6 months for the study duration: CBC with differential, Chemistry panel 20, and urinalysis and pregnancy test (for females with childbearing potential). Additionally, laboratory monitoring (CBC, chemistry panel with liver function tests) will be performed every 3 months after initiation of dosing of idebenone for the first year of treatment and every 6 months thereafter.

All adverse events occurring within 1 month following the last administration of the study medication must be recorded on the Adverse Event Form irrespective of severity and seriousness, and whether or not they are considered related to the study medication. Additionally, all serious adverse events (SAE) brought to the attention of the investigator during the period starting from the day of performance of the first study procedure to the telephone interview on month 25, must be recorded and reported to the FDA in accordance with federal regulations and NIH procedures. Any SAE reported by the patient after month 24, will be subjected to expedited reporting only if judged to be related to the study treatment by the Investigator.

The collection of complete and accurate information is of paramount importance to allow a full evaluation of SAEs. Each SAE will be properly documented and followed up until the event is resolved, subsided, stabilized, disappeared or is otherwise explained or the study patient is lost to

follow-up. Recurrent episodes, complications, or progression of the initial SAE will be reported as follow-up to the original episode, regardless of when the event occurs. Follow-up of reportable SAEs will be submitted to the FDA, IRB and Santhera Pharmaceuticals (Switzerland) Ltd. according to the same timelines mandatory for initial reports. An SAE that is considered completely unrelated to one previously reported, will be reported separately as a new event.

NINDS will provide Santhera Pharmaceuticals (Switzerland) Ltd. with copies of all Serious Adverse Drug Reaction reports concurrently with their submission to the FDA, including copies of any warning letters or other information affecting the safety and/or well-being of human subjects in research conducted under this CTA.

9.2 Toxicity tables/criteria to be used

Toxicity will be assessed according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 (Publish date August 9, 2006). A copy of the Common Terminology Criteria for Adverse Events version 3.0 can be downloaded from http://ctep.cancer.gov/reporting/ctc_v30.html.

9.2.17 Definition of Adverse Event (AE)

An AE "is *any unfavorable and unintended diagnosis, symptom, sign (including an abnormal laboratory finding), syndrome or disease which either occurs during the study, having been absent at baseline, or, if present at baseline, appears to worsen*." An AE is a term that is a unique representation of a specific event used for medical documentation and scientific analyses.

9.2.18 Severity of Adverse events

Grade refers to the severity of the AE. The CTCAE v3.0 displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline:

Grade 1 Mild AE
Grade 2 Moderate AE
Grade 3 Severe AE
Grade 4 Life-threatening or disabling AE (SAE)
Grade 5 Death related to AE (SAE)

Assessment	Definition
1 = Mild	Discomfort noted, but no disruption of normal daily activities; slightly bothersome; relieved with or without symptomatic treatment
2 = Moderate	Discomfort sufficient to reduce or affect normal daily activity to some degree; bothersome; interferes with activities, only partially relieved with symptomatic treatment.
3 = Severe	Discomfort sufficient to reduce or affect normal daily activity considerably; prevents regular activities; not relieved with symptomatic treatment.

9.2.19 Definition of Serious Adverse Event (SAE)

A serious adverse event is any untoward medical occurrence or effect at any dose, that:

- results in death,
- is life threatening,
- results in persistent or significant disability/incapacity,
- requires in-patient hospitalization‡ or prolongation of existing hospitalization,
- results in cancer,
- is a congenital anomaly/birth defect in the offspring of a study subject,
- is deemed, by the investigator, an important or serious medical event that may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above should be considered serious (i.e., intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.)

9.2.20 Assessment of causality

Every effort should be made by the investigator to explain each adverse event and assess its causal relationship, if any, to the study medication. The degree of certainty with which an adverse event can be attributed to the study medication (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the event can be understood in terms of one or more of the following:

- Reaction of similar nature having previously been observed with this type of medication.
- The event having often been reported in literature for similar types of medication.
- Subject's underlying clinical state or other medical conditions
- Concomitant agents and/or therapies

The causal relationship, if any, to study medication will be defined by one of the following terms:

Assessment	Definition
Definitely	There is suspicion of a relationship between study medication and AE (without determining the extent of probability); there are no other more likely causes and study medication is suspected to have contributed to the AE
Probable	AE cannot be reasonably explained by other factors (i.e. clinical condition, environmental/toxic factors or other treatments)
Possible	AE can be reasonably explained by other factors (as mentioned above)
Unlikely	AE occurs within an unusual time frame of administration of study medication and can also be reasonably explained by other factors (as mentioned above)
Unrelated	There is no suspicion that there is a relationship between study medication and adverse event, there are other more likely causes and study medication is not suspected to have contributed to the AE

9.2.21 Treatment of adverse events

Treatment of any AE is at the sole discretion of the investigator and according to current available best treatment. The applied measures will be recorded in the patient's chart.

1.2 Criteria for individual subject withdrawal

A subject *must* permanently discontinue study drug treatment for any of the following reasons:

1. The subject becomes pregnant (pregnancy test will be performed for female patients with child bearing potential during study visits as indicated in section 7.5.6). If a patient becomes pregnant, treatment must be *immediately* discontinued. The pregnancy must be reported to the NIB (treating physician/research nurse) and to the IRB immediately. Information about the subject, the subject's pregnancy, the outcome of the pregnancy, and the status of the infant at 8 to 12 weeks of age will also be collected.
2. The subject desires to discontinue study drug treatment under this protocol. Patients have the right to withdraw from the study at any time and for any reason. The investigator also has the right to withdraw patients from the study in the event of an intercurrent illness, adverse events, treatment failure, protocol violations, administrative reasons, or other reasons.
3. 1st MS safety criterion: Worsening of more than two points on the EDSS scale *(Kurtzke 1983)* compared to baseline, confirmed one month later on an extra follow-up visit. The treatment will be discontinued, but the patient will be followed off therapy to collect all predetermined outcome measures as per "intention to treat" analysis.
4. 2nd MS safety criterion: The average number of new CEL (which represents a measure of MS-related brain inflammatory activity) increases after initiation of idebenone therapy 3 standard deviations above the average number of CEL during pre-treatment baseline or for patients with no CEL observed on MRIs collected during baseline period (expected to be majority of PP-MS patients), the number of CEL recorded on a single follow-up MRI reaches 10 CEL (total). Treatment will be discontinued, but the patient will be followed off therapy to collect all predetermined outcome measures as per "intention to treat" analysis.
5. Laboratory safety criteria: ALT (SGPT) or AST (SGOT) more than three times the upper limit of normal during regular laboratory monitoring and remains more than three times the upper limit after one week of cessation of idebenone dosing. Any other highly abnormal laboratory finding that is deemed critical by an investigator and that persists for 1 week after cessation of drug dosing.

The reasons for discontinuation of the study drug must be recorded in the subject's Clinical Center patient file. Patients discontinuing dosing will be followed for an additional 2 months. If discontinuation was because of an adverse event, the patient will be followed until the event is resolved or stabilized. If the discontinuation was because of pregnancy, the subject will be followed until after the birth.

10. OUTCOME MEASURES

10.1 Primary outcome measure

The primary outcome measure of the IPPOMS is the rate of disability progression, assessed with the Area Under the Curve (AUC) of the CombiWISE scores during the 2-year treatment period. The CombiWISE data collected during the 1-year pre-treatment period will be utilized by including both the pre-treatment disability progression (AUC of CombiWISE scores during the pre-treatment period) and severity of the disability (CombiWISE score at pre-randomization baseline) as covariates in the statistical analysis.
CombiWISE was developed based on the pre-determined analysis of 58 candidate outcomes collected in 1 year pre-treatment phase in 1 training (IPPOMS1) and 2 validation (IPPOMS2 and RIVITALISE) cohorts, as described in detail in recent publication (Kosa, Ghazali et al. 2016).CombiWISE is a continuous scale ranging from 0 to 100, has strong correlation with EDSS (i.e., scale used for regulatory approval of MS drugs; rho = 0.9805, $p<0.0001$, n=303) and has the strongest power among all 58 tested outcomes (Kosa, Ghazali et al. 2016).

10.2 Secondary outcome measures

10.2.1 Neuroimaging outcomes

1. Inhibition of individualized rates of enlargement of ventricular volume: effect of idebenone versus placebo on individualized rates of enlargement of segmented volume of lateral and 3rd ventricles

10.2.2 Clinical/functional outcomes

1. Progression in EDSS-plus, as defined in (Cadavid, Cohen et al. 2017). EDSS-plus response will be analyzed using a cox proportional hazards model.
2. Progression of lower extremity disability as assessed by 25 foot walk component of MSFC
3. Progression of upper extremity/fine motor movements disability as assessed by non-dominant hand 9 hole peg test component of MSFC
4. Progression of neurological disability as assessed by Scripps NRS
5. Progression of neurological disability as assessed by EDSS

10.3 Exploratory outcome measures

10.3.1. Neuroimaging

1. Progression of retinal nerve fiber thinning as detected by OCT (comparing idebenone to placebo)

10.3.2. Clinical

1. Progression in cognitive dysfunction as assessed by Symbol Digit Modality Test (comparing Idebenone to placebo)
2. Progression of neurological disability as assessed by MSFC

10.3.3. Biological/immunological

1. Analysis of changes in CSF albumin quotient between idebenone and placebo (ROS are known to disrupt endothelial tight junctions; which may be measured as increase in CSF albumin quotient)
2. Analysis of changes in CSF biomarkers of activated/pro-inflammatory microglia/monocytes (sCD14)
3. Analysis of changes in CSF lactate/pyruvate ratio, as a biomarker of extra-mitochondrial glucose metabolism
4. Analysis of changes in CSF growth differentiation factor 15 (GDF15), as a putative biomarker of mitochondrial dysfunction
5. Analysis of changes in CSF neurofilament light chain (NF-L), a biomarker of axonal damage

11. STATISTICAL ANALYSIS

11.1 Data acquisition and processing

All clinical, neuroimaging volumetric and biomarker data will be collected sequentially and analyzed in a blinded fashion from coded samples. Data will be acquired prospectively and transcribed to the research database. For the imaging biomarker of ventricular volume the analysis will be performed only after completion of baseline or treatment periods, because the images need to be co-registered to the first acquired image. For biomarker data that can be acquired from cryopreserved biological samples, baseline and treatment data points will be evaluated simultaneously, to limit effect of inter-assay variation. Every effort will be made to have single rater/investigator to acquire one type of quantifiable clinical, neuroimaging and biomarker data for the entire cohort. Codes will be broken only after all pre-specified quantifiable data constituting primary and secondary outcomes are collected and recorded in the database.

11.2 Statistical analyses of outcome measures

Further details of the statistical analysis (e.g. definition of analysis populations) will be defined in a Statistical Analysis Plan which will be finalized before the database lock and opening of the treatment code.

Introduction

a) For data collected only at 2 time-points (i.e. single collection during pre-treatment baseline and single collection at 1 year of therapy), such as CSF data, we will calculate for each individual %-change between baseline and therapy time-points
b) For data collected every 6 months (i.e. clinical data and quantitative brain MRI data) we will calculate area under curve (AUC) for 3 data points obtained during pre-treatment baseline period and compare it to AUC for 5 data points obtained during the treatment period.

The rational for using AUC (as opposed to linear regressions) is explained in detail in Figure 3:

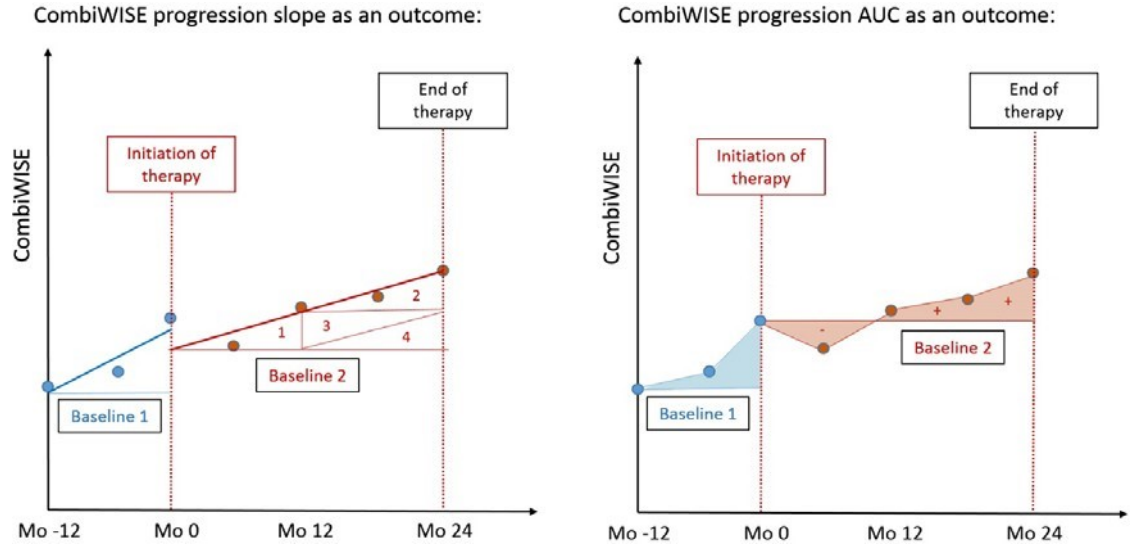

Figure 3: There are two possible ways how changes in outcomes collected every 6 months (e.g., primary outcome: CombiWISE) can be analyzed: 1. As a change in regression slopes (left panel) or 2. As a change in AUC (right panel). There are two major problems with regression slopes: First, the baseline pre-treatment period slope is derived only from 3 measurements. Because these measurements are spread equally apart, the least squares linear regression slopes are calculated only from 1st and 3rd measurement, whereas the middle (2nd) measurement affects only the intercept. Consequently, even though we have three baseline measurements, only two of them would be de-facto utilized for final outcome comparison. Furthermore, as depicted in the left panel, if the drug has both neuroprotective effect (which decreases slope) and promotes structural or functional repair (which decreases intercept), comparing slopes would de-facto ignore the latter potentially important mechanism of action (MOA). In contrast, measuring changes in disability progression between untreated and treated period using AUC (right panel) eliminates both stated disadvantages of progression slopes. This method uses all measured data and correctly deals with the improvements in disability by subtracting parts of the curve that are below the baseline (i.e. CombiWISE measure at the initiation of therapy) from the AUC part that is above the baseline.
The only problem with AUC is unequal length of the compared periods: while pre-treatment baseline period has 1-year length, the treatment period for IPPOMS trial has length of 2 years. It may be intuitive to divide 2-year AUC period by 2 to obtain equivalent yearly measurements, but that is incorrect. As depicted in the left panel, if the progression slopes were linear, the AUC derived from 2-year period needs to be divided by 4 to get equivalent yearly AUC progression. We have validated correctness of this adjustment by analyzing blinded 2 year CombiWISE data from 50 patients who finished 2 years of study and by comparing average AUC derived from splitting Year 1 and Year 2 of this longitudinal cohort, versus calculating AUC from the entire 2-year period. We observed that these two measurements strongly correlate with each other (r^2=0.905) with following linear regression formula:
Y = -0.77 + 3.96*X, where X is average yearly AUC and Y is 2-year AUC measured in the same patient.
Consequently, this mathematical analysis confirmed that 2-year AUC must be divided by 4 to obtain equivalent yearly change. The intercept (-0.77) represents improvement in disability, which is incorrectly ignored when the treatment period is split into two yearly AUCs.

Statistical Hypothesis

The hypothesis to be tested for the primary efficacy endpoint CombiWISE is:

> H_0: There is no difference between idebenone and placebo in the disability progression during the 2-year treatment period.

The alternative superiority hypothesis is

> H_A: The disability progression in idebenone-treated patients is slower than in the placebo-treated patients during the 2-year treatment period.

In addition to the difference between the treatment groups, the within-group changes in each treatment group will be evaluated by comparing the disability progression during the pre-treatment period to the progression during the treatment period.

The analysis for the primary outcome measure CombiWISE will be performed in all randomized patients using a two-sided type I error rate of $\alpha = 0.05$.

Primary Analysis of the Primary Outcome Measure

The AUCs of the CombiWISE scores during the 2-year treatment period will be analyzed using an Analysis of Covariance (ANCOVA) model with the AUC of the pre-treatment CombiWISE scores, Baseline (Month 0) CombiWISE score and Baseline age as covariates.

The incomplete data in the CombiWISE scores during the 2-year treatment period will be managed with the single imputation algorithm defined in Section 5.3.

The within group changes will be tested using paired t-test within each treatment group. For this analysis, to compare the 1-year pre-treatment period changes to 2-year treatment period changes, the treatment period AUC values will be divided by 4.

Sensitivity Analyses of the Primary Outcome Measure

1. Random coefficient regression model with random intercept and slope will be fitted to the response data. All CombiWISE scores will be included as response variables in the model. In order to model random intercept and slope for pre-and post-treatment separately, factor period (pre vs. post) will be created: pre -treatment (Month -12 to 0) vs. post-treatment (Month 0 (+1 day) to 24). Exact days from the first visit, instead of month will be used as Time in the model. In addition to the random slopes and intercepts, the model will include the fixed effect for treatment group (idebenone or placebo), period (nested within treatment), interaction between Time and period (nested in treatment) and covariates: Baseline (Month 0) CombiWISE score and Baseline age. The interaction between Time and period (nested within treatment) will be used to examine the hypothesis of four slopes are same (slopes for placebo group at pre- and post-treatment, slopes for idebenone group at period pre-and post-treatment). The pairwise comparisons of the four slopes or intercepts,

such as slope (or intercept) at post-treatment for idebenone group vs. that for placebo group, and slope (or intercept) for idebenone group at post-treatment vs. that at pre-treatment period can be constructed and performed using the statement "estimate". This analysis includes only the observed CombiWISE scores as response variables and as the model can manage incomplete data, no imputation will be done.

2. Mixed Model for Repeated Measures (MMRM) will be fitted to the response data. The observed CombiWISE scores from all scheduled post-baseline visits (Month 6, 12, 18 and 24) will be used as response variables in the model. The model will include visit, treatment group (idebenone or placebo) and the interaction between visit and treatment group as fixed factors. The Baseline (Month 0) CombiWISE score, baseline age and the rate of decline in the CombiWISE scores during the pre-treatment period will be used as covariates in the model. Both the overall treatment difference at all visits (Months 6, 12, 18 and 24 post-randomization) and the treatment difference separately at each visit will be estimated from the model. The overall treatment difference will be tested based on the fixed factor for the treatment group and the visit-specific treatment differences will be tested with contrasts derived from the fixed factor for treatment group and the interaction term between visit and treatment group. The focus of this analysis will be on the early treatment difference observed at Month 6 post-randomization and the treatment difference at the last study visit (Month 24 post-randomization). An unstructured covariance structure will be applied for the MMRM. The denominator degrees of freedom will be computed using the Kenward-Roger method. The covariate for the rate of decline will be calculated separately for each subject from the CombiWISE scores observed during the pre-treatment period using a random coefficient regression model with random intercept, random slope and time (exact number of days since the first assessment) as an explanatory factor.

3. Multiple Imputation (MI) assuming data missing at random (MAR) will be done to compare idebenone to placebo. MI techniques based on Pattern Mixture Models (PMM) will be applied in this sensitivity analysis. This methodology will structure data based on the missing data patterns. The method will be based on a missingness pattern having a monotone structure, i.e. if among the observations during the 2-year treatment period one CombiWISE score is missing, all subsequent scores after this missing value will also be treated as missing. For patients with intermittent missing values, before performing MI based on the PMM, it will be necessary to create a monotone missingness pattern. Intermittent missing values will be imputed using the Markov Chain Monte Carlo (MCMC) methodology which assumes a multivariate normal distribution over all variables included in the imputation model. This first MI step is planned to be repeated 1000 times, creating 1000 different datasets with a monotone missing data structure. Seed value of 1995 will be used in the MI procedure. The imputation is based on the missing at random (MAR) assumption, i.e. the missing data are assumed to follow the same model as the other patients in their respective treatment arm.

   After this, the remaining missing data will be imputed using a method for monotone missingness, also based on the MAR assumption. Thus, for each of the 1000 created dataset with a monotone missing data pattern, missing values will be imputed based on a sequential procedure reflecting the monotone missing data pattern. Patients with the first missing value occurring at Month 3 will have their missing Month 3 value replaced by an imputed value from a regression model with treatment group, Month 0 CombiWISE score, the pre-

treatment slope and baseline age as explanatory variables. In the next step, patients with their Month 6 value missing will have their missing Month 6 value replaced by an imputed value from a regression model with all factors defined above and Month 3 value as explanatory variables. Similar procedure will be used to replace the missing values at all subsequent visits.

The imputed datasets generated with the approach described above do contain only non-missing values and are used as input in the model for the sensitivity analysis of the primary outcome variable. MMRM similar as described in Sensitivity Analysis 2 will thus be run on each of the 1000 generated imputed datasets and the difference between the treatment groups will be estimated. Finally, the results from these analyses will be combined to derive an overall estimate of the treatment difference. In addition to the estimates, corresponding 95% confidence intervals and p-values will be calculated.

4. Multiple Imputation assuming data missing not at random (MNAR) will be done to compare idebenone to placebo. Control group based assumption (Copy Reference imputation) will be used, i.e. the trajectories of the patients are assumed to follow the placebo group trajectories after the discontinuation. Methods similar to the procedure described above will be used to generate monotone missing data. After this, the missing data will be imputed sequentially for each visit (first Month 3, followed by all subsequent visits). Only the data from the control group (placebo group) will be used as input for each imputation of both treatment groups.

Secondary Endpoints

Continuous variables will be analyzed using random coefficient regression models and/or MMRMs similar to the one defined above for the primary outcome variable

Categorical Endpoints will be analyzed using cox proportional hazards models, with treatment group, baseline values (if applicable) and baseline age as covariates.

11.3 Handling of missing/unobtainable data

All efforts will be made to collect a complete set of data by employing 1-2 week flexibility in scheduling and repeating inadequate quality MRI scans.

With the exception of the primary endpoint (AUCs) and the sensitivity analyses, for continuous and categorical endpoints, no data imputation will be made and missing data will be handled by the models itself.

The following single imputation method is applicable for handling of missing data to calculate AUCs of CombiWISE scores and MRI data.

If particular data points are missing for reasons other than inability to perform the test (i.e. because of disability) we will replace the missing data according to following algorithm:

a. For data obtained every 6 months (i.e. clinical data and brain MRI data), the missing time point will be substituted by the average of 2 adjacent time-points: i.e. 6 months before and 6 months after the missing time-point. If the last time-point is missing (i.e. month 24), we will substitute the data for this time-point by the average of 2 preceding time-points.
b. For data obtained once at baseline and once at treatment phase (i.e. CSF), the missing data cannot be replaced and the patient will be eliminated from analysis.

Handling data missing because the patient was unable to perform the test due to disability: this may happen for clinical tests such as timed 25 foot walk (25FW), 9 hole peg test (9HPT) and PASAT. These data will be calculated using the following recommendations from scoring instructions for the MSFC:

a. 25FW: the inability to perform 25FW will be substituted by the largest Z-score in the MSFC Task force database (i.e. with the slowest time of any patient in the combined dataset used by the Task Force in its published meta-analysis). The largest Z-score in the Task Force dataset is 13.7, therefore, for a subject who could not complete the 25FW $Z_{leg,\ average} = -13.7$ will be used.
b. 9HPT: the inability to perform 9HPT will be coded as 777 and the following Z-score calculation formula will be applied:
$Z_{arm,\ trial\#} = [(1/777 – \text{Baseline mean } (1/9HPT)]/\text{Baseline SD } (1/9HPT)$
c. PASAT: In the event an individual patient cannot complete PASAT-3 due to disability, a score of 0 will be assigned.

For missing data for CombiWISE calculation, the CombiWISE formula (Kosa, Ghazali et al. 2016) specifies handling of the inability to perform either 25FW or non-dominant hand 9HPT as a separate variable.

11.4 Original Power analysis and sample size calculation

Assumptions for the initial sample size calculation were:

1) Rate of development of CNS atrophy in early PP-MS patients is equivalent, or greater than the rate of development of brain atrophy in RR-MS patients and similar to rate of development of brain atrophy in SP-MS patients *(Fox, Jenkins et al. 2000)*
2) Rate of development of brain atrophy in PP-MS patients varies considerably between individuals, ranging from +1.8%/year to -3.6%/year (Mean -1.03%, SD 1.3%) for BPF and from +1.7%/year to -4.2%/year (Mean -1.50%, SD 1.6%) for grey matter fraction *(Sastre-Garriga, Ingle et al. 2005)*
3) Within 5 years of follow-up, the rate of development of brain atrophy, ventricular atrophy, cervical cord atrophy and the rate of accumulation of T2LV and T1LV seem to be significantly more stable intra-individually than inter-individually *(Ingle, Stevenson et al. 2003)*, although the intra-individual coefficient of variation values are not provided in this publication
4) Due to these inter-individual differences in the rate of accumulation of brain atrophy, the reported sample size estimates in SP-MS patients utilizing changes in brain atrophy detected by SIENA methodology applied to 1.5T MRI scans, indicates that to detect 50% therapeutic effect in a therapeutic trial of 2 year duration with 80% power and 5% significance, the minimum number of subjects is 33 per arm *(Altmann, Jasperse et al. 2008)*. The relevant data from this recent publication using SIENA methodology for calculation of whole brain atrophy in SP-MS

patients by Altmann, Jasperse et al. are summarized in the table below (selected conditions for current trial are highlighted):

Duration of Therapy	Expected therapeutic effect:	90% power				80% power		
		30% Th effect	40% Th effect	50% Th effect		30% Th effect	40% Th effect	50% Th effect
1 year	Min# subj/arm	212	120	77		158	89	57
2 years	Min# subj/arm	123	69	45		92	52	33
3 years	Min# subj/arm	107	60	39		80	45	29

Collecting at least 12 months of pre-treatment baseline volumetric MRI data (i.e. rate of development of brain atrophy, gray matter atrophy, ventricular enlargement and spinal cord atrophy) and clinical data will allow us to calculate individualized rates of CNS tissue destruction and disability progression. Based on the data described under 1)-3), employing such individualized rates of development of CNS tissue destruction for the determination of therapeutic effect between active drug and placebo is expected to significantly increase the power for detection of group differences, effectively decreasing the number of subjects necessary for demonstrating therapeutic efficacy of an experimental neuroprotective therapy (Figure 2). Additionally, employing more sensitive methodology (3T magnet strength) and novel analyses (e.g. volumetric analysis of entire cervical spinal cord) may further increase power for detection of group differences.

However, NDU did not have any longitudinal data on a PP-MS cohort that could be utilized for exact sample size analysis and the only longitudinal data that were published at the inception of this trial and could be utilized for sample size calculation were those based on whole brain atrophy as detected by SIENA methodology. Therefore, we used published sample size estimates for the SP-MS patients *(Altmann, Jasperse et al. 2008)* and targeted patient accrual to reach 66 treated patients (33 per arm).

In 2016 we performed and published pre-determined analysis of the 58 outcome measures (see section 11.5) collected in 1 year pre-treatment baseline period on first ≥30 IPPOMS patients and validated our findings in the 2 validation cohorts consisting of 34 remaining IPPOMS patients and 29 SP-MS patients from RIVITALISE trial (Kosa, Ghazali et al. 2016). This analysis demonstrated that above-stated assumptions were incorrect, that brain atrophy measured by SIENA technology was no more sensitive than clinical outcomes. Instead, based on this pre-defined analysis we selected CombiWISE as primary outcome and brain ventricular atrophy measured by LesionTOADS methodology as secondary outcome.

11.5 Selection of primary outcome measure

Based on the analysis of data from pre-randomization baseline period for the first 30 patients

Based on higher resolution of 3T versus 1.5T MRI scans and some indication from studies, either published or reported at conferences, that show that alternative measures, such as e.g. gray matter atrophy or MRS may be more sensitive than whole brain atrophy in detecting CNS tissue damage longitudinally *(Fisher, Lee et al. 2008)*, we will employ an adaptive trial design that will allow us to

select most robust (i.e. most sensitive and most accurate) primary outcome measure for the final analysis.

Specifically, we will analyze MRI and clinical/paraclinical quantitative data when 30 patients reach month 0 (i.e. will complete pre-randomization baseline period)(Kosa, Ghazali et al. 2016). From this analysis we will calculate the rate of progression of CNS tissue destruction as assessed by MRI and clinical biomarkers defined in Section 10.2, for individual patients and for the entire cohort. Because SIENA methodology for detection of progression of brain atrophy, which is currently utilized as the default primary outcome measure, calculates progression of brain atrophy as a %-age of baseline brain tissue, we will perform the same type of analysis for every other defined outcome; i.e. we will quantify the biomarker at month -12 (baseline) and months -6 and 0 and will express the values measured at months -6 and 0 as a %-age of the baseline value (i.e. assigning 100% to the value measured at month -12). For the 1st level of analysis, we will compare all outcome measures based on the measurements collected at month 0 (see Figure 4A for explanation). For each biomarker (i.e. outcome measure) we will calculate the z-score as the average change from baseline divided by the standard deviation (SD). Biomarkers with the most robust change from baseline and lowest spread of values will have the highest z-score. Figure 4A shows 3 hypothetical biomarkers: Biomarker 1 has on average the lowest magnitude of change from baseline (i.e. low sensitivity) and relatively high spread (i.e. low accuracy), leading to the lowest z-score. Biomarker 2 has the most robust change from baseline (i.e. high sensitivity), but also the widest spread of values (i.e. lowest accuracy), resulting in low z-score. Biomarker 3 has an intermediate change from baseline (i.e. intermediate sensitivity) but very low spread of values (i.e. high accuracy), resulting in the highest z-score. Biomarker 3 would be selected as the primary outcome measure.

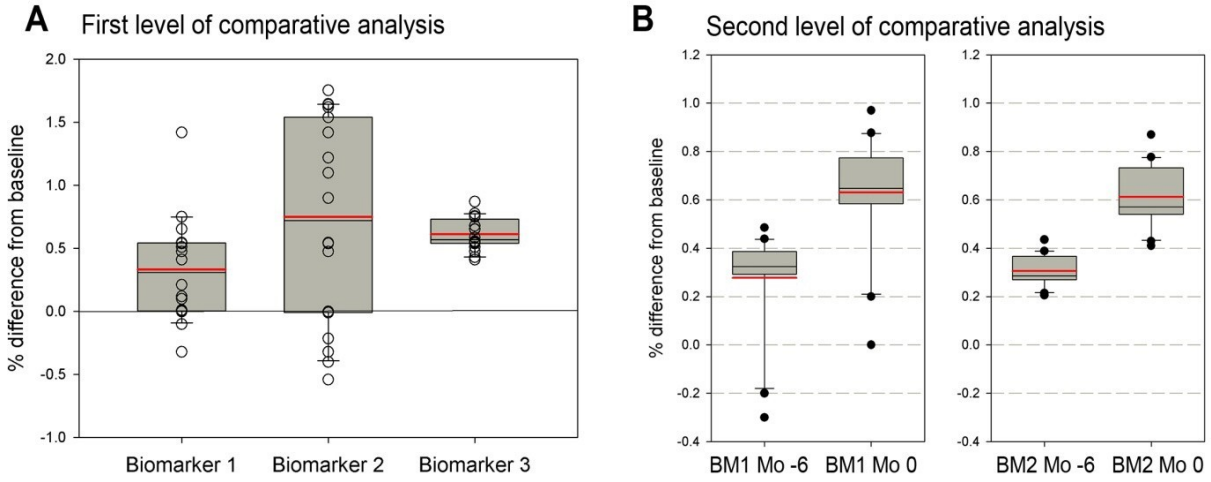

Figure 4:
A/ First level of comparative analysis: all outcome measures will be expressed as %-age of baseline values for all 30 patients. We will calculate z-scores for all outcome measures as Average (30 changes from baseline)/SD and select the biomarker with largest z-score as primary outcome measure.
B/ Second level of comparative analysis: if two biomarkers had identical or very similar z-scores in the first level of analysis, we would evaluate z-scores based on data collected at -6 months using identical methodology.

If we encounter a situation in which two or several biomarkers have identical or very similar z-scores in the first level of analysis, we will then evaluate these biomarkers based on data collected at month -6 (i.e. at Mo -6; Figure 4B).

The logic of choosing to compare z-scores rather than the simpler selection of the biomarker giving the most robust difference from baseline is as follows: the absolute difference of the longitudinal measurements of a biomarker from its baseline value is the combination of biological progression of the disease and of any technical inaccuracy of measurement. From the biological standpoint, PP-MS is a progressive disease – patients may have periods of stabilization, but in contrast to RR-MS, there are no periods of improvement. Therefore, if in some patients we measure improvement from baseline, we can assume this is most likely due to technical inaccuracy of measurement, than due to the biology of this disease. Because technical errors should be random (i.e. may result in apparent improvements as much as in exaggerated progression) a greater spread of biomarker values between patients would likely reflect greater technical measurement errors. Therefore, using standard deviation as a denominator will ensure selection of an outcome measure that combines the greatest sensitivity for detecting CNS tissue destruction and the greatest accuracy of measurement.

If, based on this analysis, we identify an outcome measure that is more sensitive and more precise than whole brain atrophy measured by SIENA methodology, we will select this new measure as the primary outcome measure.

This analysis was performed and published, including measurements of z-scores *(Kosa, Ghazali et al. 2016)*. We have compared total of 58 clinical, imaging, electrophysiological and optical coherence tomography outcomes. In the first IPPOMS cohort (which ended up being 35 patients because we lost some MRI outcomes due to technical issues such as poor quality of scans and the protocol stipulated minimum of 30 patients per outcome) we observed that total of 15 outcomes reached statistical significance based on un-adjusted p-values (See Table 2 in the *(Kosa, Ghazali et al. 2016)*). We then validated these 15 outcomes for their ability to reliably detect yearly MS disease progression in 2 independent validation cohorts: IPPOMS2 cohort (n=34) and RIVITALISE cohort (n=29). Seven out of 15 outcomes validated statistically-significant change in both independent validation cohorts, when properly adjusting for multiple comparisons. Surprisingly, the default primary outcome for IPPOMS protocol, brain atrophy measured by SIENA methodology was not validated. While six MRI biomarkers (ventricular volume and 5 diffusion-tensor imaging [DTI] markers) validated statistically-significant change in both validation cohorts, our enthusiasm for these outcomes was lowered by observation that only one of them, ventricular atrophy, showed any correlation with clinical outcomes. This measure had mild correlation with 2 cognitive scales (PASAT and SDMT) and with a MS functional composite (MSFC) scale. However, this correlation was observed only in the cross-sectional paradigm, which benefited from a broad range of disabilities present in merged untreated progressive MS cohort (n=98). In contrast, we observed absolutely no correlation between any MRI outcome and any clinical measure in 1-year longitudinal paradigm – in other words, change on MRI biomarkers did not correlate with change in any clinical outcome. The article explains in length why this is so, documenting poor signal-to-noise ratio (SNR) of even best performing MRI biomarkers for the level of change observed in the 1-year longitudinal MS data in comparison to scan-re-scan variability observed in MRI technical controls (i.e. healthy donors scanned twice at each scanner).

Because of this we concluded that MRI outcomes utilized in small Phase II trial will be unlikely to predict change on clinical outcome (used for Phase III trial), which is a definition of a “surrogacy”. Therefore, we sought alternative outcome. We noticed that clinical scales were much better correlated, even though they too had relatively low SNR. One way to decrease the noise of the measurement is to use repeated measure analysis. Therefore, we hypothesized that to the degree to

which clinical scales reflect overlapping biology (i.e. measure overlapping neurological disability) to that degree they represent repeated measure analysis. Thus, rationally combining clinical scales would allow us to differentiate between disability caused by a structural lesion (which would affect multiple clinical scales congruently) from the performance noise, which would have random distribution among clinical scales. We have tested this hypothesis by designing Combinatorial Weight-Adjusted Neurological Clinical Scale (CombiWISE version 1), where we selected contributing clinical scales and adjusted their "weights" in final formula proportionally to z-scores (defined in the IPPOMS protocol and measured in the first [IPPOMS1] cohort). After we validated that CombiWISE v1 outperforms all other clinical and MRI biomarkers, we used statistical learning based on random permutations of the modeling cohort, to mathematically optimize CombiWISE outcome *(Kosa, Ghazali et al. 2016)*.

Not only mathematically-optimized CombiWISE outperformed all remaining 57 studied outcomes, but it also retained highly statistically significant correlations with majority of clinical outcomes, including EDSS that is currently used for regulatory approval of MS drugs. However, in comparison to EDSS, which is ordinal scale from 0-10, CombiWISE is a continuous scale from 0-100. One point change in EDSS corresponds on average to 7.50 point change in CombiWISE with a standard error of 0.10, making CombiWISE significantly more sensitive (and specific) measure of neurological disability *(Kosa, Ghazali et al. 2016)*.

11.6 Accrual number request

Up to 85 subjects are planned to be recruited based on current sample size calculation, to account for 20% drop-out and final number of treated subjects 33 per arm (66 total). These recruitment numbers were already achieved and interim analysis of the outcomes showed enhanced, rather than diminished power of new primary outcome (CombiWISE) in comparison to original default primary outcome (Brain atrophy measured by SIENA).

11.7 New power analysis

If the above-described analysis of secondary outcome measures identifies a new primary outcome, we will conduct a new power analysis for the selected new primary outcome, using two-sample t-test with estimates of mean and standard deviation of changes from baseline collected on the first 30 enrolled patients. Based on this new power analysis, we will amend the protocol to indicate the final accrual number request.

The new power analysis for CombiWISE, EDSS and ventricular volume change has been published for both within-group and between-group designs (Kosa, Ghazali et al. 2016). Using absolute change in the CombiWISE AUC outcome determined from the pre-treatment baseline data in IPPOMS cohort, following power calculation for AUC was derived:

Drug effect	untreated	treated	difference	Actual Power	N Pairs		
50%	51.24	25.62	25.62	0.807	28	Distribution	Normal
45%	51.24	28.18	23.06	0.806	34	Method	Exact
40%	51.24	30.75	20.50	0.802	42	Number of Sides	2
35%	51.24	33.31	17.94	0.807	55	Standard Deviation	46.2
						Correlation	0.5

30%	51.24	35.87	15.37	0.801	73	Nominal Power	0.8
25%	51.24	38.43	12.81	0.804	105	Null Difference	0
20%	51.24	40.99	10.25	0.802	162	Alpha	0.05

This demonstrates that substituting default primary outcome (Brain atrophy measured by SIENA *(Altmann, Jasperse et al. 2008)*) with CombiWISE primary outcome will significantly enhance power of the IPPOMS trial from estimated 80% of power to detect at least 50% drug effect to more than 80% power to detect at least 40% drug effect. Additionally, while brain atrophy measured by SIENA does not correlate with clinical outcomes, CombiWISE has strong, highly significant correlations with EDSS, which is used for regulatory approval of MS treatments, both in cross-sectional and longitudinal paradigms (i.e. yearly change in CombiWISE correlated with yearly change in EDSS). Therefore, CombiWISE can predict efficacy on EDSS outcome, but does so in considerably smaller cohorts and/or trials of shorter duration *(Kosa, Ghazali et al. 2016)*.

12. HUMAN SUBJECT PROTECTION

12.1 Subject selection

The investigational nature and objectives of this trial, the procedures and treatments involved, as well as the attendant risks, discomforts, and potential benefits will be carefully explained to the patient. A signed consent form will be obtained by the principal investigator or an associate investigator. It will be carefully explained to patients that they may withdraw from the study at any time, for any reason.

All adult PP-MS patients fulfilling all inclusion criteria and for whom none of the exclusion criteria are applicable, irrespective of gender or race are included in the trial. The age limits are 18-65 years, inclusive. The rational for this age limit is explained in detail under Section 4.7. The upper age limitation is scientifically justified in this very early stage of clinical trial; if idebenone proves its therapeutic efficacy in this optimally selected patient population, further studies will be required to determine the exact age limit of its efficacy in this disorder. This will permit to use more equitable populations in later phases of clinical development of idebenone for PP-MS.

12.2 Justification for exclusion of children

Patients under the age of 18 are excluded since the incidence of MS in this age group is extremely low and PP-MS is virtually non-existent. Consequently, insufficient numbers of patients in that age range would be available to provide reliable data.

12.3 Study safeguards

Because the effects of idebenone therapy on pregnancy and breastfeeding are unknown, patients able to become pregnant or able to father a child will be required to use appropriate methods of contraception for the trial duration and all women able to become pregnant will be evaluated with a pregnancy test every 6 months and before any MRI. Women over age 55 who have not had a period for one year will be considered menopausal and will not need pregnancy testing or contraception.

Women under the age of 55 will undergo pregnancy testing and will be required to use appropriate methods of contraception for the trial duration, unless there is a history of surgical menopause.

12.4 Qualifications of investigators

The NIB clinical team has extensive experience with Phase I/II experimental therapeutic trials in MS. This team has performed 7 Phase I/II clinical trials in MS in the past 10 years. The PI, Dr. Bibiana Bielekova is a board-certified neurologist with full clinical privileges. She underwent clinical research training (Core Course in Clinical Research at NIH, October 1997-June 1998 and FDA's Clinical Investigator Training Course, November 7-9, 2011) and served as an investigator on 5 Phase I/II clinical trials at NIH and 2 Phase II clinical trials at the University of Cincinnati. Dr. Bielekova will be responsible for all aspects of the research. All pre-planned immunological, cellular and molecular biomarker studies will be performed in her laboratory and under her direction. Dr. Bielekova will not obtain informed consent or serve as a treating or evaluating physician due to a conflict of interest, and because thanks to her supervision of biomarker studies, she may become inadvertently unblinded to treatment allocation.

Lead associate investigator Alison Wichman is a board certified neurologist. She has been credentialed in the NIH Clinical Center continuously since 1982. She has expertise in many aspects of clinical research both as a clinician, and in management roles related to research ethics, regulations, human subject protection, and SOP development Mary Alice Sandford is a certified nurse practitioner with over 30 years of experience working with patients with neuroimmunological disorders, including Multiple Sclerosis. Dr. Tanya Lehky is board-certified neurologist with full clinical privileges. All above-mentioned investigators will have direct clinical contact with patients and all can obtain informed consent.

Jenifer Dwyer is registered nurse specialized in MS clinical care. Laura Kannaian is a registered nurse with multiple years of experience including with MS patients. Rosalind Hayden is a registered nurse with experience in research and regulatory support. She will be involved in regulatory submissions, and will also supervise patient scheduling. The above-mentioned investigators will have direct clinical contact with patients and they will not obtain informed consent.

Drs. Lehky, Wichman, and Ms. Sandford will be responsible for patient care and assessment, collection of clinical and functional outcome measures and overseeing clinical safety.

Dr. Bhagavatheeshwaran is a staff scientist with the NIB. Dr. Bhagavatheeshwaran is responsible for MRI acquisition and analysis. Carlo Pierpaoli, MD, PhD is an internationally recognized expert in diffusion tensor imaging (DTI) analysis and tool development. He has developed TORTOISE, which is a state of the art DTI processing software. He will participate in the analysis of DTI images by testing clinical utility of the new DTI tools developed in his laboratory. Elena Romm is biologist with long-term experience in sample collection and processing. She will supervise collection, processing and storage of all biological samples: CSF, serum, apheresis/whole blood samples for PBMC collection and skin biopsy. She will serve as the primary laboratory contact and will keep updated database of biological sample collection and storage. Dr. Bhagavatheeshwaran, Dr. Pierpaoli, and Ms. Romm will not obtain informed consent.

13. BENEFITS

13.1 Direct Benefit

Participants may receive direct therapeutic benefit from participation in this study

13.2 Indirect Benefit

The study will yield generalizable knowledge about the drug and disease state and will aid in developing future neuroprotective therapeutic trials in MS patients

14. SUMMARY/CLASSIFICATION OF RISK:

For the study as a whole

The risk is classified as more than minimal risk.

This is a reasonable risk in relation to the anticipated potential therapeutic benefit in a patient population for which there are currently no therapeutic agents with proven benefit and for obtaining generalizable knowledge that will facilitate more rapid screening of novel neuroprotective agents in low-inflammatory progressive MS subtypes.

15. CONSENT DOCUMENTS AND PROCESS

Prior to any testing under this protocol, including screening or pre-treatment tests and evaluations, written informed consent will be obtained from the subject in accordance with local practice and regulations. Study investigators will obtain informed consent, as noted in the Qualifications of Investigators section.

The background of the proposed study and the benefits and risks of the procedures and study will be explained to the subject. A copy of the informed consent document signed and dated by the subject will be given to the subject. Confirmation of a subject's informed consent will also be documented in the subject's medical records prior to any testing under this protocol, including screening or pre-treatment tests and evaluations.

On occasion, it may be necessary to obtain informed written consent by a phone discussion process. It may be necessary, for example if a participant has completed screening under protocol 09-N-0032, and has met all inclusion criteria except the washout period from a previous treatment. In some cases, waiting for completion of the washout phase may result in their being too old to enroll in this study. As most of our participants are traveled from other states, it is impractical to fly participants back to NIH solely for the consent process. For telephone/written consent, the following process will be followed.

This study and its consent form will be reviewed with the participant in person at their 09-N-0032 screening visits. Their questions will be answered. If they are interested in participating, they will be provided with an unsigned copy of the consent form to take home with them, or a copy will be mailed to them with a postage paid addressed return envelope. Once they meet all eligibility criteria (including completion of a washout period if needed), they will be contacted by telephone by someone authorized to obtain consent for the study. They will be asked to have a witness with them at the time of the telephone call. The consent form information will be reviewed again over the

phone and any further questions answered. If they agree to participate, the patient will sign and date the consent form, and have a witness sign and date the consent form. They will return the signed consent form to NIH. After the investigator who obtained consent signs the consent form, a complete signed copy will be sent to the participant. The original, signed consent form will be sent to medical records and an additional copy maintained in research records. The consent process will be documented in the medical and research records.

Information that is gained through this study will be available to the participating patients.

Consent forms are attached.

16. DATA AND SAFETY MONITORING

16.1 Monitoring plan for the study as a whole

This study will be monitored by a Data and Safety Monitoring Board (DSMB). Dr. Mary Kay Floeter is a board-certified neurologist with full clinical privileges. She will serve as the Independent Medical Monitor. Dr. Floeter is independent of NIB and will be involved in crucial decision making regarding clinical issues that may arise during this trial. We are instituting an NIB independent medical monitor as a way to mitigate Dr. Bielekova's conflict of interest (COI). Dr. Bielekova, the PI on the study, is co-inventor on an NIH patent related to the use of idebenone and as such will receive patent royalty payments.

16.2 DSMB plans

16.2.3 The proposed members of the DSMB are as follows

Mitchell T. Wallin, MD (DSMB chair) and Walter Royal, MD from MS Center of excellence, East, VA, Baltimore, MD, Carlos Mora, MD from Georgetown University MS center and Prof. Ludwig Kappos, MD from MS research group, University Hospital Basel, Switzerland

16.2.4 Role of DSMB

a. Monitor/review AE on yearly basis and SAE within 15 days of receiving the SAE report.

16.2.5 Proposed meeting frequency/ schedule

The DSMB will meet on a yearly basis via teleconference. Yearly AE data and clinical data will be collected and provided to the DSMB for review. Additionally, all SAEs will be communicated to the DSMB within 7 days of occurrence.

1.3 ***Criteria for stopping the study***

All SAEs will be communicated to the DSMB. Depending on the nature of the SAE and its potential relationship to the study medication, the DSMB may request unblinding of the treatment allocation for any patient that suffers SAE(s) and will decide on further action.

17. Quality Assurance (QA)

17.1 Quality assurance monitor

A Contract Research Organization (CRO) will monitor this protocol.

17.2 Quality assurance plan

On-site monitoring will be carried out by the CRO. An initial visit will be conducted by the CRO, following final approval of the protocol by the IRB and FDA. During the initial visit, the study team and the monitor determined the frequency of monitoring visits. The frequency was set at yearly. The sponsor via the CRO, will be responsible for providing adequate oversight of the investigation to ensure adequate protection of the rights, welfare, and safety of human subjects and the quality and integrity of the resulting data.

18. ADVERSE EVENTS REPORTING

The Principal Investigator is responsible for detecting, documenting, and reporting unanticipated problems, adverse events (AEs), including serious adverse events (SAEs), and deviations in accordance with NIH policy, IRB requirements, and federal regulations. Relatedness to the research of all serious adverse events will be determined by the PI in consultation with the CD.

Serious unanticipated problems, serious adverse events (including deaths) that are not unanticipated problems, and serious protocol deviations will be reported to the IRB and CD as soon as possible and in writing on the Problem Report Form not more than 7 days after the PI first learns of the event, unless immediate reporting is waived for specific serious adverse events as noted below. Not serious unanticipated problems and not serious deviations will be reported to the IRB and CD as soon as possible and in writing on the Problem Report Form not more than 14 days after the PI first learns of the event.

All adverse events, deviations, and unanticipated problems will be summarized and reported at the time of Continuing Review.

The following expected Serious Adverse Events will not be reported to the IRB immediately and within 7 days unless they occur at a rate or severity greater than expected:
Hospitalization for urinary tract and kidney infections
Hospitalization for falls resulting in injury

These SAE's will be summarized at the time of continuing review. Serious adverse events occurring at a greater severity or frequency than expected will be reported as Unanticipated Problems as delineated above. The expected severity and frequency will be based upon each patient’s pre-randomization history (baseline).

The NINDS, holder of the investigator-IND, or her/his representative is responsible for submitting reportable SAEs to the FDA under its private IND application, in accordance with Federal and NIH requirements. The NINDS is also responsible for providing Santhera Pharmaceuticals (Switzerland) Ltd. with copies of all Serious Adverse Drug Reaction reports concurrently with their submission to the FDA, including copies of any warning letters or other information affecting the safety and/or well-being of human subjects in research conducted under this CTA.

Santhera Pharmaceuticals (Switzerland) Ltd. is responsible, in collaboration with United BioSource Corporation (UBC) Geneva, for the processing of reportable SAEs received from the NINDS or her/his representatives. Santhera is also responsible for the submission of those reportable SAEs to Health Authorities (other than the FDA), Ethics Committees and Investigators taking part in studies with the same active moiety, as required by regulations. Moreover, Santhera Pharmaceuticals (Switzerland) Ltd. will transmit to the NINDS all reports of Serious Adverse Drug Reaction occurring in Santhera-sponsored studies and associated with the same active moiety, as well as any other information altering the safety profile of the study drug.

19. ALTERNATIVES TO PARTICIPATION OR ALTERNATIVE THERAPIES

There are currently no therapeutic alternatives with proven therapeutic benefit for PP-MS patients.

20. PRIVACY

All research activities will be conducted in as private a setting as possible.

21. CONFIDENTIALITY

21.1 For medical records

Medical records will be maintained in the NIH Clinical center and released according to NIH regulations and Health Insurance portability and Accountability Act of 1996 (HIPAA) guidelines.

21.2 For research data

Research data will be anonymized and locked in file cabinets if in paper form or in password protected electronic databases maintained on NINDS secure server or on encrypted computers at the NIH. Only study investigators will have access to research data. Anonymized data and results may be shared with Santhera Pharmaceuticals for research purposes and for drug filing with the FDA.

21.3 For stored samples

Coded biological samples will be stored in secure freezers and liquid nitrogen tanks at the NIH. Anonymized samples may be made available for future testing in this or other laboratories following the guidelines of the Office of Human Subjects Research.

22. CONFLICT OF INTEREST/TECHNOLOGY TRANSFER

NIH guidelines on conflict of interest have been distributed to all investigators.

Dr. Bielekova has identified a conflict of interest related to this study. She is one of the co-inventors on an NIH patent related to the use of idebenone as therapeutic agents in humans. This conflict of interest is properly disclosed in the protocol and in the consent form.

To resolve this conflict-of-interest, we have instituted following safeguards:

- Dr. Bielekova will not obtain informed consent and will not serve as the treating or evaluating physician on this protocol.

- Mary Kay Floeter, MD, a senior NINDS neurologist who is not part of the NIB, will serve as the Independent Medical Monitor under this protocol.
- The independent DSMB will monitor the study.

No other investigators identified any additional conflicts of interest.

A clinical trial agreement (CTA#2009-0004) has been established with Santhera Pharmaceuticals through the NIH/NINDS office of technology transfer (OTT). This agreement specifies that Santhera will provide idebenone without restriction for the clinical study as outlined. All collected raw data will be the sole property of NINDS. Summary data will be made available to Santhera Inc. for regulatory purposes and for stock exchange purposes. Santhera Inc. can use these summary data for other purposes only after consultation with NINDS and only under confidentiality agreement.

23. RESEARCH AND TRAVEL COMPENSATION

Enrolled patients will not be compensated for time and research-related inconveniences.

Enrolled patients will be reimbursed for travel and lodging according to NINDS guidelines (travel form as attachment).

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25. ATTCHAMENTS/APPENDICES

25.1 Flow chart

	Pre-treatment Baseline Period (Month -12 - 0)					Idebenone Treatment Period (Month 0-24)			
	Month -12	Month -11	Month -10	Month -6	Month 0 (2 days)	Month 6	Month 12 (2 days)	Month 18	Month 24 (2 days)
Clinical									
Clinical evaluation	√			√	√	√	√	√	√
Inclusion/Exclusion criteria	√				√				
Urinalysis/pregnancy	√	√		√	√	√	√	√	√
Clinical Lab work	√				√	√	√	√	√
Safety Lab work						Every 3 months for the first year and Every 6 months for the second year			
Imaging									
MRI brain 3T (Q 6mo)	√			√	√	√	√	√	√
OCT (Q 12 mo)	√				√		√		√
Immunology									
Research Blood (≤ 60ml)			√		√		√		√
Lymphocytapheresis *	√						√		√
Lumbar puncture	√						√		
Lithium Heparin (5mL) *optional*			√				√		
Skin biopsy	√								

NB: all studies to be completed within 4 weeks +/- date indicated with exception of baseline lymphocytapheresis, lumbar puncture and skin biopsy, which can be performed anytime during pre-treatment baseline period.
*120 cc of whole blood may be collected in the place of Lymphocytapheresis if there is a contraindication.

25.2 Eligibility checklist

Inclusion criteria

- ☐ PP-MS as determined by the 2005 modification of McDonald's diagnostic criteria *(Polman, Reingold et al. 2005)*
- ☐ Age between 18-65 years (inclusive)
- ☐ EDSS measure of neurological disability from 1 (no disability, clinical signs only) to 7 (ambulatory with bilateral support) *(Kurtzke 1983)*
- ☐ Able to provide informed consent
- ☐ Willing to participate in all aspects of trial design and follow-up
- ☐ Agreeing to commit to the use of reliable method of birth control (i.e. hormonal contraception (birth control pills, injected hormones, vaginal ring), intrauterine device, barrier methods with spermicide (diaphragm with spermicide, condom with spermicide) or surgical sterilization (hysterectomy, tubal ligation, or vasectomy) for the duration of treatment arm of the study
- ☐ Not receiving any immunomodulatory/immunosuppressive therapies for a period of at least 3 months before enrollment in the study
- ☐ No exposure to idebenone, coenzyme-Q_{10} or other dietary supplements (such as antioxidants, mitochondrial-function promoting supplements or vitamins in excess of 3 times recommended daily doses) for a period of at least 1 month before enrollment in the study

Exclusion criteria

- ☐ Alternative diagnoses that can explain neurological disability and MRI findings
- ☐ Clinically significant medical disorders that, in the judgment of the investigators can cause CNS tissue damage or limit its repair, or that would expose the patient to undue risk of harm or prevent the patient from completing the study
- ☐ History of hypersensitivity reaction to idebenone or coenzyme Q_{10}
- ☐ Pregnant or lactating women. All women of child-bearing potential must have negative pregnancy test prior to the treatment phase of the study.
- ☐ Abnormal screening/baseline blood tests exceeding any of the limits defined below:
    - Serum alanine transaminase or aspartate transaminase levels greater than 3 times the upper limit of normal values
    - Total white blood cell count < 3,000/mm^3
    - Platelet count < 85,000/mm^3
    - Serum creatinine level > 2.0 mg/dl or eGFR (glomerular filtration rate) <30
    - Positive pregnancy test
- ☐ Patients who are receiving any immunosuppressive therapies (including cytostatic agents) due to the concern that these drugs may contribute to neurodegeneration or limit CNS repair

23.3 Case Report Forms (CRFs)

Trial data will be captured using the NIH Clinical Research Information System (CRIS) in the structured Neuroimmunology note. Additional data are captured in CRIS that may be useful in verifying the compliance to the study protocol, such as appointment dates, orders, adverse event documentation, etc.

APPENDIX D:

23.4 Rating scales

23.4.1 Expanded Disability Status Scale (EDSS)

0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS. Fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters.
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; May require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of day; has some effective use of arms retains some self care functions
9.0	Confined to bed; can still communicate and eat.
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

23.4.2 Scripps NRS

Scripps NRS **Systems Examined**		**Maximum points**	**Normal**	**Degree of impairment**		
				Mild	**Mod.**	**Severe**
Mentation and Mood:		10	10	7	4	0
Cranial nerves:	Visual acuity	21	5	3	1	0
	Fields, Discs, Pupils		6	4	2	0
	Eye movements		5	3	1	0
	Nystagmus		5	3	1	0
Lower cranial nerves:		5	5	3	1	0
Motor:	RU	20	5	3	1	0
	LU		5	3	1	0
	RL		5	3	1	0
	LL		5	3	1	0
Deep Tendon Reflexes:	UE	8	4	3	1	0
	LE		4	3	1	0
Babinski: R&L (2 for each)		4	4	-	-	0
Sensory:	RU	12	3	2	1	0
	LU		3	2	1	0
	RL		3	2	1	0
	LL		3	2	1	0
Cerebellar:	UE	10	5	3	1	0
	LE		5	3	1	0
Gait: Trunk and balance:		10	10	7	4	0
Bladder/Bowel/Sexual dysfunction:		0	0	-3	-7	-10
Scripps NRS total score:						

23.5 Modified McDonald's Diagnostic Criteria for PP-MS

(Polman, Reingold et al. 2005)

1) One year of disease progression (retrospectively or prospectively determined)
2) *Plus* two of the following:
   a. Positive brain MRI (≥9 T2 lesions or ≥4 T2 lesions with positive VEP)
   b. Positive spinal cord MRI (≥2 focal T2 lesions)
   c. Positive CSF (isoelectric focusing evidence of oligoclonal IgG bands or increased IgG index, or both)

As with RR-MS, the alternative diagnoses that could explain insidious progression of neurological disability or MRI/CSF findings need to be searched for and ruled out before the diagnosis of MS can be concluded.

23.6 Recruiting advertisements

Do you have Primary Progressive Multiple Sclerosis?

If so, you may qualify for an NIH research study.

The Neuroimmunology Branch (NIB) of the National Institutes of Health is conducting a study to investigate the efficacy of an oral experimental drug in primary progressive multiple sclerosis. The study will be conducted at the NIH Clinical Center in Bethesda, Maryland, on an outpatient basis.

We are seeking participants:

- ages between 18-65
- diagnosis of Primary Progressive Multiple Sclerosis
- not taking any immunomodulatory drugs

The study involves a one year baseline after which participants will receive the medication or placebo for 2 years. Medical evaluations, MRIs, and blood work will be performed at scheduled intervals during the 3-year study. The visits will last 2-5 hours each and will be every month the first 3 months and then every 6 months for the remainder of the study.
There is no cost for participation.
Travel reimbursement will be provided.

Please call 301-496-0064 for more information about participating in this study. Please refer to study number 09-N-0197. www. ClinicalTrials.gov

Do you have Primary Progressive Multiple Sclerosis?

Researchers at the NIB are seeking adults ages 18-65 with a diagnosis of Primary Progressive Multiple Sclerosis to participate in a randomized, placebo controlled, double blind study investigating the efficacy of Idebenone in this disease. Participation will include medical evaluations, MRI, bloodwork, and lumbar puncture performed at the NIH Clinical Center on an outpatient basis.

Q. What's involved in the study?

A. This study is a randomized, placebo controlled, double blind study. Individuals who qualify and decide to participate will be randomly assigned to receive the study drug or a placebo. Neither the individual nor the investigators will know which patients are taking the study drug, until the conclusion of the trial. All individuals participating in the trial will be monitored at scheduled intervals, and at the conclusion of the trial, based on clinical and MRI assessments, it will be determined if the study drug is effective in this disease.

Q. How may I benefit?

A. If this drug proves to be effective, the progression of your disease may slow down or even improve.

Q. Are there risks involved?

A. Over 8 million individuals have been treated with Idebenone for other neurological conditions, including Alzheimer's disease. Idebenone has been found to be well tolerated and safe. The most common side effects reported have been gastrointestinal symptoms, including nausea, diarrhea and loss of appetite.

Q. Will this cost me any money?

A. No, you will not be charged for any part of the study.

Q. How much time does the study take?

A. The study will last 3 years. During the initial screening period, you will need to be seen several times over approximately a 3 month period. After that, you will need to return approximately every 6 months. Over the 3 years, you will have a total of approximately 15 visits. Visits may vary in length, but are usually from two to five hours long. We will try to schedule visits at times that are most convenient for you.

Q. How will my primary neurologist be involved?

A. You will remain in the care of a non-NIH neurologist who will manage any symptoms and guide treatment decisions that are unrelated to the clinical trial. NIH may make recommendations for your care, but will not act as your primary neurologists. All management related to the clinical trial, such as MRIs and bloodwork, will be performed at the NIH.

Dear …….,

Thank you for your interest in our research. We are beginning a new research study to explore the efficacy of an experimental drug, idebenone, in primary progressive multiple sclerosis. This study will take place at the National Institutes of Health, within the National Institute of Neurological Disorders and Stroke (NINDS). The study will be a randomized, blinded, placebo-controlled trial.

We are seeking patients age 18-65 who have a diagnosis of primary progressive multiple sclerosis and who are not on immunomodulatory treatment. The study will last three years. Upon entering the study, patients will undergo serial MRI studies and clinical examinations which will be performed monthly for 3 months. Following this, patients will enter a pre-treatment phase of 12 months duration, during which clinical visits, MRI imaging and blood work will be performed every 6 months. Patients will then be randomized to receive treatment or placebo, with continued monitoring by clinical exam, MRI and bloodwork at scheduled intervals. In addition to the MRI imaging and clinical exams, participating patients will undergo a spinal tap at the time of enrollment and again after one year of treatment.

Idebenone (2,3-dimethoxy-5-methyl-6-(10-hydroxydecyl)-1,4-benzoquinone) is a synthetic analogue of coenzyme Q10, which is an indispensable constituent of the mitochondrial electron-transport chain and also cell membrane antioxidant. Idebenone has been extensively studied as a potential therapeutic agent for neurological diseases, including Alzheimer's disease, Huntington's disease, Friedrich's ataxia and multi-infarct dementia. In these clinical trials, in which a variety of doses and dosing regimens were employed, idebenone was found to be safe and well tolerated. In these studies, the most frequently cited adverse effects that occurred more often in the idebenone group were gastrointestinal symptoms such as anorexia, nausea, and diarrhea.

If you know of any patients who might qualify for this study, we would greatly appreciate if you could provide the patient and their family member/caregiver with a copy of the enclosed advertisement so that they can contact us. We also plan to meet with as many professionals as possible to describe this study in further detail. Please contact us at 301-496-0064 if you would like further information regarding this study.

Sincerely,

Dear …….,

Thank you for your interest in our research. We are beginning a new study to explore the efficacy of an experimental drug, idebenone, in primary progressive multiple sclerosis. This study will take place at the National Institutes of Health, within the National Institute of Neurological Disorders and Stroke (NINDS). The study will be a randomized, blinded, placebo-controlled trial; this means that patients who qualify and decide to participate will either receive the study drug or a placebo, and neither the patient nor the investigators will know who is on the drug and who is not until the end of the study. Assignment to receive drug or placebo will be random.

A key feature of MS is demyelination, which is the loss of the insulating myelin sheath which usually protects brain and spinal cord cells and allows them to communicate effectively with other brain and spinal cord cells. One of the hypotheses explaining the continuous worsening of symptoms in progressive forms of MS is that when demyelination occurs, brain cells require much more energy to maintain their function. Eventually, the cells are unable to maintain these high energy demands and die.

The drug we will be investigating in this clinical trial, idebenone, can improve the function of mitochondria – which are the power houses of cells, responsible for generating energy. As such, idebenone can improve energy production and use in cells, and may be able to prevent the loss of nerve cells in MS. In addition, idebenone is a potent antioxidant, which may also help in reducing the loss of nerve cells.

Idebenone is an oral medication and has been extensively studied in several neurological diseases. In these clinical trials, idebenone was found to be safe and well tolerated. In these studies, the most frequent side effects were gastrointestinal symptoms such as loss of appetite, nausea, and diarrhea.

If you have a diagnosis of primary progressive multiple sclerosis, are between18-65 years of age, and are not on any immunomodulatory treatment, you may be eligible. The study will last three years. Upon entering the study, you would undergo a series of MRIs and clinical examinations which will be performed monthly for 3 months. This is part of a pre-treatment phase of 12 months, during which clinical visits, MRI imaging and blood work will then be performed at 6 months and one year. This baseline period is critical in order to be able to interpret the final results of trial. After this one year baseline, you would be randomized to receive treatment or placebo, and would have continued monitoring by clinical exam, MRI and bloodwork at scheduled intervals. In addition to the MRI imaging and clinical exams, all participating patients will undergo a lumbar puncture at the time of enrollment and again after one year of treatment.

If you would like further information regarding this study, please call us at 301- 496-0064. Travel or transportation assistance may be discussed with a member of our research team.

Sincerely,

09-N-0197 Multiple Sclerosis
Social Media
Facebook and Twitter Draft
Date: 01/24/2012

NIH researchers are studying primary-progressive multiple sclerosis to see if they can stop or slow symptoms with certain medications. Learn more: clinicaltrials.gov, study #09-N-0197 or call the NIH Clinical Center Patient Recruitment office Toll-Free: 1-800-411-1222 or TTY: 1-866-411-1222.

23.7 MS Patient Questionnaire

Attached in PTMS.

23.8 Investigator's Brochure

Attached as pdf file or hard copy

23.9 Clinical trial agreement (CTA)

Attached as pdf file or hard copy