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Design, rationale, and baseline characteristics of the randomized double-blind phase II clinical trial of ibudilast in progressive multiple sclerosis

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ABSTRACT

Background: Primary and secondary progressive multiple sclerosis (MS), collectively called progressive multiple sclerosis (PMS), is characterized by gradual progression of disability. The current anti-inflammatory treatments for MS have little or no efficacy in PMS in the absence of obvious active inflammation. Optimal biomarkers for

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phase II PMS trials is unknown. Ibudilast is an inhibitor of macrophage migration inhibitor factor and phosphodiesterases-4 and −10 and exhibits possible neuroprotective properties. The goals of SPRINT-MS study are to evaluate the safety and efficacy of ibudilast in PMS and to directly compare several imaging metrics for utility in PMS trials.

Methods: SPRINT-MS is a randomized, placebo-controlled, phase II trial of ibudilast in patients with PMS. Eligible subjects were randomized 1:1 to receive either ibudilast (100 mg/day) or placebo for 96 weeks. Imaging is conducted every 24 weeks for whole brain atrophy, magnetization transfer ratio, diffusion tensor imaging, cortical brain atrophy, and retinal nerve fiber layer thickness. Clinical outcomes include neurologic disability and patient reported quality of life. Safety assessments include laboratory testing, electrocardiography, and suicidality screening.

Results: A total of 331 subjects were enrolled, of which 255 were randomized onto active study treatment. Randomized subjects were 53.7% female and mean age 55.7 (SD 7.3) years. The last subject is projected to complete the study in May 2017.

Conclusion: SPRINT-MS is designed to evaluate the safety and efficacy of ibudilast as a treatment for PMS while simultaneously validating five different imaging biomarkers as outcome metrics for use in future phase II proof-of-concept PMS trials.

1. Background

Multiple sclerosis (MS) is a chronic demyelinating disease affecting the brain, spinal cord, and optic nerves. The precise etiology of MS is still unknown, although several pathological processes including inflammation, demyelination, and axonal damage contribute to the disease manifestations. MS most commonly starts as an episodic disorder called relapsing remitting MS (RRMS), with the majority of untreated patients eventually developing gradual progressive disability, which marks the secondary progressive form of MS (SPMS) [1]. About 15% of patients do not have initial phase of episodic relapses and instead present with gradually progressive disability, which is a form of MS called primary progressive MS (PPMS). Together, SPMS and PPMS comprise progressive multiple sclerosis (PMS) which affects about 1 million people worldwide [2].

While there are multiple disease modifying therapies (DMT) for RRMS, no effective therapy is currently available for PMS in the absence of obvious active inflammation. Treatment of PMS is therefore primarily limited to symptomatic and supportive care, making PMS a significant unmet clinical need in neurologic care.

Ibudilast is a small molecule phosphodiesterase inhibitor which is currently approved in Japan and other Asian countries for treatment of asthma and post-stroke symptoms at a 20–30 mg/day dosage. While ibudilast is not yet approved outside of Asia, development is ongoing for neurological conditions including MS, neuropathic pain, and drug addictions [3–6]. Ibudilast penetrates the CNS well and selectively inhibits the pro-inflammatory cytokine macrophage migration inhibitory factor (MIF) [7] and certain cyclic nucleotide phosphodiesterases at clinically relevant plasma and CNS concentrations [8]. Both systems have been implicated in neurodegeneration and disease progression in animal models and their inhibition leads to neuroprotective effects [9–15]. The potential neuroprotective effects of ibudilast were suggested in a phase II trial in RRMS, where it slowed the progression of brain atrophy and decreased the proportion of gadolinium-enhancing lesions converting into T1 black holes [3]. Taken together, the potential neuroprotective effects of ibudilast makes it an attractive candidate therapy for PMS.

Development of effective therapies for PMS has been limited by the lack of validated biomarkers for use in Phase II trials. Currently, whole brain atrophy (WBA) is the most widely utilized outcome measure for phase II PMS trials [16,17]. WBA can be detected at all stages of MS disease and represents a summation of the destructive pathologic processes in MS. Many studies show significant correlations between WBA and overall clinical disability, cognitive impairment [18–22], depression [23], fatigue [24,25], and quality of life [26,27]. However, WBA is a relatively crude measure of overall brain injury, lacking granularity to characterize localized injury.

Better metrics of MS injury are needed to screen potential therapies for PMS. Candidate markers should correlate with tissue injury, be dynamic over the course of disease, and be easily implemented in a standardized fashion in multi-centered clinical trials. Potential metrics include a few novel MRI measures (magnetization transfer ratio (MTR), diffusion tensor imaging (DTI), and cortical atrophy) and optical coherence tomography (OCT), which is a non-invasive imaging tool for measuring retinal nerve fiber layer (RNFL) thickness in the retina.

2. Methods

The NeuroNEXT 102 (NN102)/**S**econdary and **P**rimary p**R**ogressive **I**budilast **N**euroNEXT **T**rial in **M**ultiple **S**clerosis (SPRINT-MS) is a randomized, placebo-controlled, Phase II clinical trial evaluating the effect of ibudilast and assessing the utility of other imaging biomarkers in PMS.

3. Study organization

The clinical trial is a collaborative study conducted by the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT). Started in 2011, NeuroNEXT is an initiative of the National Institute of Neurological Disorders and Stroke (NINDS) designed to accelerate development of therapies for neurological diseases through partnerships with academic institutions, non-profit organizations, and industry. The core of NeuroNEXT comprises a Clinical Coordinating Center (CCC, which is located at the Massachusetts General Hospital, Boston, MA), a Data Coordinating Center (DCC, which is located at the University of Iowa, Iowa City, IA), and 25 academic medical centers across the US. Central to the function of NeuroNEXT is external peer-review to ensure high quality scientific rigor; centralized ethics oversight, which is provided through the Central Institutional Review Board (CIRB) at Massachusetts General Hospital; a single master clinical trial agreement for each participating clinical site, through which all NeuroNEXT trials at that site are contracted; and operational support by the NINDS. Details about NeuroNEXT structure have been published previously [28]. Funding for the SPRINT-MS trial is primarily through a competitive peer-reviewed grant issued by the NINDS, with additional funding provided by the National MS Society and Medicinova, which holds intellectual property rights to ibudilast.

4. Overall trial design

The primary objective of SPRINT-MS is to evaluate the safety, tolerability, and activity of ibudilast (100 mg/day taken orally) compared to placebo in subjects with PMS. The trial is designed as a multicenter, randomized, double-blind, placebo-controlled, parallel-group study.