SPRINT-MS/NN 102 Phase II Trial of Ibudilast in Progressive MS: Baseline Characteristics

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Background

Progressive multiple sclerosis (PMS) is a gradually progressive form of MS characterized by neurodegeneration and insidious progression of disability. Treatments for PMS are limited to stopping active inflammation and provide minimal slowing of progressive disability. Thus, PMS represents a significant unmet clinical need in neurologic care. Complicating matters, the currently-recommended outcome measure for phase II PMS trials is whole brain atrophy, which has limited sensitivity and granularity in characterizing brain tissue integrity and the potential benefit of neuroprotective therapies.

Ibudilast is a small molecule inhibitor of macrophage migration inhibitor factor (MIF) and phosphodiesterases (PDE)-4 and -10. Ibudilast has been used in Japan and other Asian countries for asthma and cerebrovascular disorders for over 20 years. Ibudilast has extensive in vitro, animal model, pre-clinical and clinical studies suggesting potential neuroprotective efficacy. A phase II trial in relapsing MS provided evidence for neuroprotection as measured by slowed brain atrophy and reduced conversion of gadolinium-enhancing lesions into T1 holes.[1] Both relapsing MS and neuropathic pain trials showed evidence for dose-dependent benefits.[1]

Objectives

The primary objectives of the study are:

- to evaluate the activity of ibudilast (100 mg/d) versus placebo at 96 weeks as measured by quantitative magnetic resonance imaging (MRI) analysis for whole brain atrophy using brain parenchymal fraction.
- to evaluate the safety and tolerability of ibudilast (100 mg/d) versus placebo administered orally in subjects with primary progressive multiple sclerosis and secondary progressive multiple sclerosis

The secondary objectives are to evaluate the activity of ibudilast at 96 weeks versus placebo as measured by:

- Diffusion tensor imaging (DTI) in descending pyramidal white matter tracts
- Magnetization transfer ratio (MTR) imaging in normal-appearing brain tissue
- Retinal nerve fiber layer as measured by optical coherence tomography (OCT)
- Cortical atrophy as measured by cortical longitudinal atrophy detection algorithm (CLADA)

The ***additional secondary outcomes*** are to measure the activity of ibudilast at 96 weeks versus placebo on:

- Inflammatory disease activity, as measured by T1 lesion volume, T2 lesion volume, and annualized relapse rate
- Disability, as measured by Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC-4)
- Cognitive impairment, as measured by Symbol Digit Modalities Test (SDMT) and the Selective Reminding Test (SRT)
- Quality of Life as measured by Multiple Sclerosis Impact Scale (MSIS-29, EuroQol 5 Dimensions (EQ-5D), and Short Form-36 Health Survey (SF-36)
- Neuropathic pain, as measured by Brief Pain Inventory

Methods

NeuroNEXT Network

The NeuroNEXT Network is an NIH-funded clinical trial network which aims to accelerate the development of therapies for neurologic diseases

- test promising therapeutics in phase II clinical trials

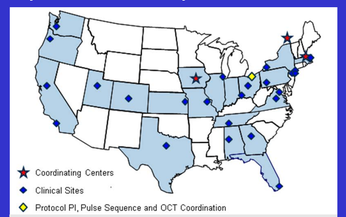

Figure 1. Location of SPRINT-MS / NN102 study sites.

Methods (cont'd)

- Accelerate drug development through an established clinical trials network
- Decrease time and cost between trial design and trial completion
- Coordinate public/private sector efforts towards neurologic diseases

SPRINT- MS: Secondary and Primary pRrogressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis

A 96-week, 250-subject, randomized, double-blind, placebo-controlled phase-II trial of Ibudilast

- Utilizing 28 sites from the NeuroNEXT network (Table 1, Figure 1),
- Supported by the NINDS, with contributions from foundation and industry
- Clinical measures: EDSS and MSFC-4
- Cognitive tests: SDMT and SRT
- Patient Reported Outcome measures: MSIS-29, EQ-5D and SF-36

Key Inclusion Criteria:

- Subjects aged 21 – 65 years, inclusive
- EDSS 3.0 – 6.5, inclusive
- Clinical evidence of disability progression in the preceding two years, as measured by any of the following
  - o EDSS worsening of at least 0.5 points
  - o 20% worsening in 25-foot walk
  - o 20% worsening in 9-hole peg test in either hand
- Concurrent MS disease modifying therapy may include interferon-beta (any preparation) or glatiramer acetate (any preparation) or none

Key Exclusion Criteria:

- Current or recent use of systemic corticosteroids
- Current use of MS disease-modifying therapies (each with specific wash-out periods) besides interferon-beta and glatiramer acetate
- Significant laboratory abnormalities
- History of malignancy (<5 years)
- Unable to complete MRI imaging to obtain high quality scan

Table 1: Clinical site and Site PIs for SPRINT-MS trial

Albert Einstein College of Medicine Yeshiva University	Corey McGraw, MD, Jerome Graber, MD
Cleveland Clinic	Daniel Ontaneda, MD
Columbia University Medical Center	Claire S. Riley, MD
Weill Cornell Medical College	Jai Perumal, MD
Emory University	Neil Lava, MD
Brigham and Women's Hospital	Christopher Severson, MD
Massachusetts General Hospital	Eric Klawiter, MD
Northwestern University	Joy Derwenskus, MD
Ohio State University	Aaron Boster, MD, Michael Racke, MD
Oregon Health and Science University	Vijayshree Yadav, MD
SUNY Upstate	Burk Jubelt, MD
SUNY Buffalo	Bianca Weinstock-Gutman, MD
SUNY Stony Brook	Patricia Coyle, MD
Swedish Medical Center - Seattle	Pavle Repovic, MD, PhD
University of Alabama at Birmingham	Khurram Bashir, MD
University of California - Davis	Mark Agius, MD
University of California - Los Angeles	Barbara Giesser, MD
University of Cincinnati	Aram Zabeti, MD
University of Colorado - Denver	Augusto Miravalle, MD
University of Kansas Medical Center	Sharon Lynch, MD
University of Miami School of Medicine	Silvia Delgado, MD
University of Pittsburgh	Galen Mitchell, MD
University of Rochester	Andrew Goodman, MD
University of Texas Southwestern Medical Center	Angela Flores, MD
University of Utah	Dana DeWitt, MD
University of Virginia - Charlottesville	Myla Goldman, MD
Vanderbilt University	Harold Moses, MD
Washington University in St. Louis School of Medicine	Robert Naismith, MD

Methods (cont'd)

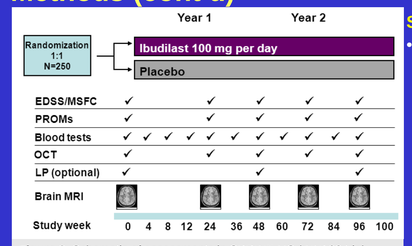

Figure 2. Schematic of assessments in SPRINT-MS / NN102 trial.

Site-Specific Requirements

- MRI scans to be performed on either GE 3T or Siemens Trio/Skyra/Prisma magnets
  - o Imaging protocol includes T1 global, T2, MTR, and 54-direction DTI
  - o Sites to submit monthly Quality Assurance scans of a standard phantom to assess scanner performance
- OCT scans to be acquired on Cirrus or Heidelberg spectral domain OCT
- Separate, blinded examiner for EDSS

Quality Control:

- Active IND with FDA (IND holder: Medicinova)
- Study coordination by Clinical Coordinating Center (Massachusetts General Hospital) and Data Coordinating Center (U. of Iowa)
- NeuroStatus certification for EDSS
- MRI acquisition coordination by NeuroRx (Montreal, Canada) and Cleveland Clinic
- Central OCT coordination by Digital Angiography Reading Center (Cleveland and New York, USA)
- Centralized clinical reading of all MRIs and OCTs for unanticipated clinical findings
- Central Institutional Review Board (Massachusetts General Hospital)

Sample size and Enrollment

Using BPFs derived from a longitudinal progressive MS dataset and assuming 10% drop-out, enrollment of 125 subjects was projected to obtain an 89% power to detect a 40% reduction in atrophy progression, and an 80% power to detect a 33% reduction in atrophy progression. An 8% screen-fail rate was projected, yielding 300 subjects to be enrolled. This enrollment projection was later revised to 334 based upon a higher-than-expected screen-fail rate.

Results

- Enrollment started in November 2013, with the majority of sites becoming activated in the first half of 2014.
- As of April 6, 2015, 311 subjects have been enrolled (104% of original goal; 93% of revised goal) and 228 have been randomized (91% of goal; Figure 3)
- Currently, 334 enrollments are projected to obtain at least 250 randomized subjects.
- Baseline characteristics of currently randomized subjects are given in Table 2.

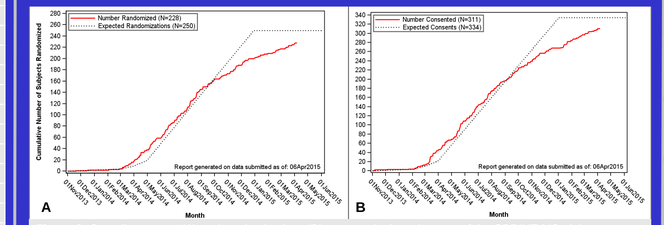

Figure 3. Overall consents (A) and randomizations (B) per month since the start of the SPRINT-MS trial.

Results

Table 2. Baseline characteristics of randomized subjects to date (n=228)

Demographics	Mean age (SD, range)	55.7 yrs (7.3; 31-65)
	Female (n, %)	122, (53.5%)
	Male (n, %)	106, (46.5%)
Race*	White (n, %)	214 (90.8%)
	African American (n, %)	9 (3.9%)
	American Indian or Alaska Native (n,%)	4 (1.8%)
	Unknown (n, %)	4 (1.8%)
Ethnicity	Hispanic (n, %)	8 (3.5%)
	Non-Hispanic (n, %)	207 (90.8%)
	Unknown (n, %)	13 (5.7%)
MS Characteristics at Screening	Mean MS duration (SD)	12 yrs (9.24)
	Primary Progressive MS (n, %)	119 (52.2%)
	Secondary Progressive MS (n, %)	109 (47.8%)
	Mean EDSS (SD)	5.4 (1.2)
	Mean 25 FW time (SD)	16.2 sec (20.3)
	Mean 9 HPT time (SD)	Dominant: 32.0 sec (15.4) Non-dominant: 40.0 sec (40.2)
Concurrent MS therapies	None (n, %)	162 (71.1%)
	Interferon-beta (n, %)	31 (13.6%)
	Glatiramer acetate (n, %)	35 (15.4%)
Lumbar Puncture (optional)	Participating (n, %)	75 (32.9%)
	Not Participating (n,%)	153 (67.1%)
MRI characteristics at baseline	T2 lesion volume (mean, SD)	9.7 cc^3 (10.0)

*More than one race may be selected

Table 3. Main reasons for screen failure

Abnormal laboratory results	**47.9%**
Unacceptable quality MRI	**16.9%**
Recent corticosteroid use	**8.5%**
No documented disease progression	**10.6%**
Unwilling to comply with study procedures	**7.0%**
Other reasons	**15.5%**
Note: total is >100% because some subjects had more than one reason.	

- To date, 71 subjects have failed screening, yielding a screen failure rate of 22.8% with laboratory abnormalities being the most common reason for screen failure (Table 3).
- Enrollment will continue until the target 250 randomized subjects is attained.

Conclusions

- The SPRINT-MS trial will both evaluate the activity and safety of a novel therapy for progressive MS and conduct a head-to-head comparison of five imaging metrics for potential use in future phase II trials of progressive MS.
- A complex clinical trial which includes advanced MRI and OCT acquisition can be successfully implemented through an academic-based clinical trial network.
- The screen-failure rate of 22.8% was higher than projected, with laboratory abnormalities accounting for half of screen failures.
- The baseline characteristics of the SPRINT-MS subject population is typical of other progressive MS trials.

References

1.Barkhof F, Hulst HE, Drulovic J, Uitdehaag BM, Matsuda K, Landin R. Ibudilast in relapsing-remitting multiple sclerosis: a neuroprotectant? Neurology. Mar 30 2010;74(13):1033-1040.

Acknowledgements: We are indebted to the staff at the clinical sites, Clinical Coordinating Center, Data Coordinating Center, University of Rochester (central laboratory and pharmacy), NeuroRx, and DARC who support the SPRINT-MS trial, and all of the MS patients who have enrolled into the trial.

Supported by National Institutes of Health (U01NS082329 to Cleveland Clinic), National Multiple Sclerosis Society (RG-5184-A-6), Medicinova (through the National Institutes of Health), and individual grants from the National Institutes of Health to the Clinical Coordinating Center, Data Coordinating Center and each of the NeuroNEXT sites.

Disclosure: Dr. Fox has received consultant fees from Biogen Idec, GlaxoSmithKline, Novartis, Questcor, Teva, and Xenoport; grant and research support from Novartis. Dr. Coffey has received personal compensation for activities with ZZ Biotech, LLC as a consultant. Dr. Cudkowicz has received consultant fees from Trophos, GSK, Biogen-Idec, Teva; served as site PI for clinical trials sponsored by Biogen-Idec and Neuraltis. Dr. Goodman received personal compensation from Acorda Therapeutics, Actelion, Biogen-Idec, Genzyme-sanofi, GW Pharma, Mylan, Novartis, Teva, and Vaccinex for consulting services; financial support for research activities from Acorda Therapeutics, Avanir, Biogen Idec, EMD Serono, Genzyme-sanofi, Novartis, Ono, Roche, Sun, Takeda, and Teva. Dr. Klawiter has received consulting fees from Biogen Idec and Mallinkrodt Pharmaceuticals; served as a site PI for a multi-center clinical trial by Roche. Dr. Naismith received consulting and speaking fees from Acorda, Bayer, Biogen, Genentech, Genzyme, EMD Serono, Novartis, Questcor, Teva; served as Associate Editor, Journal Watch Neurology; served as site PI in a clinical trial sponsored by Acorda. Dr. Matsuda, Mr. Gleason, Mr. Yankee, Ms. McGovern and Ms. McNeil report no disclosures.