SPRINT-MS/NN 102 Phase II Trial of Ibudilast in Progressive MS: Top Line Results

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Background

Ibudilast is a small molecule inhibitor of macrophage migration inhibitor factor (MIF), phosphodiesterases (PDE)-4 and -10, and Toll-like receptor 4. Ibudilast has been used in Japan and other Asian countries for asthma and cerebrovascular disorders for over 20 years. Ibudilast has 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]

Secondary and ***P***rimary p***R***ogressive ***I***budilast ***N***euroNEXT ***T***rial in ***M***ultiple ***S***clerosis (**SPRINT-MS**) is a phase II trial of ibudilast in primary and secondary progressive MS utilizing the NINDS-sponsored NeuroNEXT clinical trial network.

Objectives

Primary Outcome: Activity, safety, and tolerability of ibudilast in progressive MS, compared to placebo. The primary activity outcome was quantitative magnetic resonance imaging (MRI) analysis for whole brain atrophy using brain parenchymal fraction (BPF).

Key Secondary Outcomes: Diffusion tensor imaging of the descending corticospinal tract; magnetization transfer ratio in the normal-appearing brain tissue; retinal nerve fiber layer thickness measured by optical coherence tomography; cortical atrophy.

Secondary Outcomes: inflammatory disease activity, disability, as measured by Expanded Disability Status Scale (EDSS) and Multiple Sclerosis Functional Composite (MSFC), cognitive impairment, quality of life, and neuropathic pain.

Only a subset of results are available and presented here.

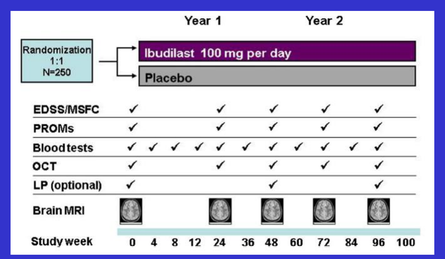
Methods

Trial Subjects

Subjects for the SPRINT-MS study were enrolled at 28 US sites and randomized 1:1 to ibudilast (up to 100 mg/day) or placebo, and followed over 96 weeks.

Inclusion criteria:

- Age 18-65 years
- PPMS or SPMS
- EDSS 3.0-6.5
- Disability worsening in prior 2 years
  May be untreated, or treated with interferon or glatiramer acetate



Statistical Plan

Modified Intent-to-Treat Analysis

- Received ≥1 dose and ≥1 MRI

Stratified randomization

- Disease type (PPMS vs SPMS)
- MS therapy (on vs off)

Analyses

- Imaging outcomes: Linear mixed effect model
- Safety and tolerability: Logistic regression or Fisher's Exact test

Results

Enrolled subjects

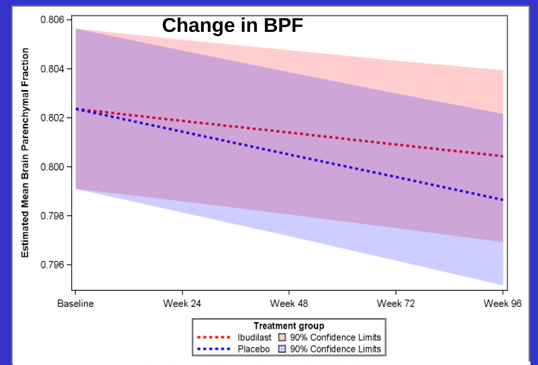
Enrollment started in November 2013 and closed in June 2015, with 331 enrolled and 255 randomized to treatment.

- 126 randomized to placebo:
  - 123 finished week 24
  - 112 finished week 96
  - 94 on treatment allocation
- 129 randomized to ibudilast:
  - 121 finished week 24
  - 108 finished week 96
  - 90 on treatment allocation

Retention rate through week 96 was 86%.

Demographics	Placebo (n = 126)	Ibudilast (n = 129)	P-value
Age (yrs)	57 (6.5)	55 (7.8)	0.02
Females	69 (55%)	67 (52%)	0.71
Caucasian	114 (91%)	122 (95%)	0.79
Disease type (% SPMS)	60 (48%)	61 (47%)	0.96
Disease duration (Y)	11.7 (9.0)	12.2 (9.3)	0.65
EDSS	5.4 (1.1)	5.4 (1.1)	0.74
DMT (IFN or GA)	40 (32%)	40 (31%)	0.90

Primary Endpoint: Whole Brain Atrophy



Estimated Rate of Annual BPF Change

Treatment Group	Estimate (90% CI)	P-Value
Ibudilast	-0.00105 (-0.00160, -0.00049)	0.040
Placebo	-0.00202 (-0.00256, -0.00147)	

Treatment with ibudilast was associated with a 48% slowing in rate of decline in BPF. Per protocol analysis gave similar results (50% reduction, p=0.045).

Key Secondary Endpoints: Magnetization Transfer Ratio & Diffusion Tensor Imaging

- Change in MTR in Normal-Appearing Brain Tissue was reduced -0.00558 for ibudilast and -0.03064 for placebo, which was a relative reduction of 82% in MTR decline.
- Change in MTR in Normal Appearing Gray Matter was reduced -0.00753 for ibudilast and -0.03210 for placebo, which was a relative reduction of 77% in MTR decline.
- No significant difference in white matter changes in transverse diffusivity (p=0.15) or longitudinal diffusivity (p=0.73), compared to placebo.

Primary Endpoint: Safety and Tolerability

Treatment-emergent Adverse Events

	Placebo	Ibudilast	p-value
Any Adverse Event	**88%**	**92%**	**0.26**
Gastrointestinal System	39%	51%	0.050
- Nausea	15%	27%	0.020
- Diarrhea	7%	16%	0.027
- Abdominal Pain	0%	5%	0.030
- Vomiting	2%	7%	0.098
Other			
- Depression	3%	9%	0.048
- Upper Resp. Tract Infection	19%	10%	0.045
- Neck Pain	3%	0%	0.058
- Skin Infection	6%	1%	0.062

Treatment-related Adverse Events

	Placebo	Ibudilast	p-value
Any Adverse Event	**48%**	**67%**	**0.002**
Gastrointestinal SOC	20%	41%	0.0003
- Nausea	9%	23%	0.004
Investigations SOC	6%	14%	0.05
Nervous System SOC	8%	16%	0.064
Skin & Subcutaneous Tissue SOC	4%	9%	0.097
Other			
- Fatigue	1%	5%	0.096
- Atrioventricular Block First Degree	3%	0%	0.058
- Neck Pain	3%	0%	0.058
- Skin Infection	6%	1%	0.062

Serious Adverse Events:

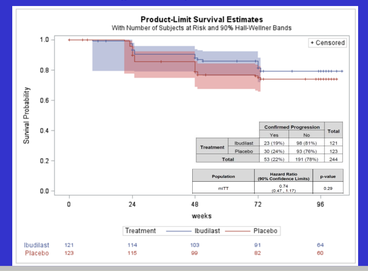
- No increased rate of SAEs, no opportunistic infections or cancer signal

Tolerability:

- 25% on placebo and 30% on ibudilast discontinued treatment (p=0.39)
- 12% on placebo and 18% on ibudilast discontinued treatment (p=0.18)

Additional Secondary Endpoint: Disability

- A blinded evaluator assessed EDSS at baseline and every 24 weeks. Time to confirmed (≥20 weeks) EDSS progression, not due to a relapse, was determined by a time-to-event Kaplan-Meier analysis using a Cox proportional hazards model.
- The hazard ratio for progression in the ibudilast versus placebo group was 0.74 with a 90% confidence interval of 0.47 to 1.17 (p = 0.29).



Conclusions

- Compared to placebo, ibudilast treatment was associated with 48% slowing in the rate of atrophy progression
- A similar benefit was seen with MTR, but not DTI
- Treatment-related adverse events were mostly gastrointestinal, as well as rash, depression, and fatigue
- No increased rate of SAEs, no opportunistic infections or cancer signal
- No statistically significant difference in tolerability, although ~5% higher discontinuation rate in ibudilast group

Additional analyses are underway

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Disclosures: See below and online abstract listing for full disclosures.