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

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Disclosures

Dr. Fox has received consulting fees from Biogen Idec, GlaxoSmithKline, Novartis, Questcor, Teva, and Xenoport; research support from Novartis. Dr. Coffey has received consulting fees from ZZ Biotech, LLC. Dr. Cudkow icz has received consulting fees from Astra Zenica, Cytokinetics, Biohaven, Denali, BiogenIdec, and Genentech. Dr. Goodman has received received consulting fees from Acorda Therapeutics, Actelion, BiogenIdec, GenzymeSanofi, GW Pharma, Mylan, Novartis, Teva, and Vaccinex for consulting services; research support from Acorda Therapeutics, Avanir, Biogen Idec, EMD Serono, Genzymesanofi, Novartis, Ono, Roche, Sun, Takeda, and Teva Neuroscience. Dr. Klawiter has received research grants from Atlas5D, Biogen, EMD Serono, and Roche. Dr. Klawiter, has received consulting fees from Acorda, Atlas5D, Biogen, Celgene, EMD Serono, Genentech, and Shire. Dr. Matsuda is the Chief medical officer of Medicinova. Dr. Naismith has received consulting fees from Acorda, Alkermes, Bayer, Biogen, EMD Serono, Genentech, Genzyme, Novartis and Teva Neuroscience. Dr. Bermel has received consulting fees from Biogen, Novartis, Genentech, and Genzyme; research support from Biogen and Novartis. Dr. Low e has received consulting fees from Siemens Medical Systems, Inc. Dr. Alvarez has received consulting fees from Biogen, Celgene, Genzume, Genentech, Novartis and TG pharmaceuticals and has received research funding from Acorda, Biogen, Genentech, Novartis and Rocky Mountain MS Center. Dr. Cohen has received consulting fees from EMD Serono, Mylan, and Novartis; research support through NU from Hoffman La Roche/Genentech, Novartis, and MedDay. Dr. Coyle has received consulting fees from Accordant, Acorda, Bayer, Biogen, Celgene, Genentech/Roche, Novartis, Sanofi Genzyme, Serono, Teva; and research support from Actelion, Alkermes, Genentech/Roche, MedDay, NINDS and Novartis. Dr. Dewitt has received consulting and speaking fees from Novartis and Teva. Dr. Flores has received consulting/speaker fees and research support from Biogen and Genentech. Dr. Goldman has received consulting fees or served on the scientific advisory board for Adamas, Acorda, Biogen, EMD Serono, ENDECE, Genzyme, and Novartis Pharmaceuticals; research support from Biogen, Medday, and Novartis. Dr. Lynch has received support from by Biogen, Teva, Novartis, Opexa, Genzyme, Roche, Genentech, Sun Pharma and Acorda. Dr. Moses has received consulting fees from BiogenIdec, Teva Neuroscience, EMDSerono, Medimmune, Novartis, Genzyme and Bayer; speaking fees from BiogenIdec, Teva Neuroscience, EMD Serono, Bayer and Genzyme. Dr. Ontaneda has received consulting fees from Biogen Idec, Genentech, Genzyme, and Merck; research support from Race to Erase MS Foundation. Dr. Racke has received consulting/speaking fees or research support from Actelion, Alkermes, Coherus Bioscience, Genentech, Novartis, TG Therapeutics and NIH. Dr. Repovic has received consulting/speaker fees from Biogen, Genzyme, Teva, EMD Serono, Acorda and Novartis. Dr. Riley has served on the advisory board for Teva. Dr. Severson has received consulting fees from BiogenIdec, Genentech and Novartis; speaking fees from Foundation of Neurologic Diseases and MS cure fund. Dr. WeinstockGuttman has received consulting and speaking fees from Biogen Idec, Teva Neuroscience, EMD Serono, Novartis, Genzyme, Sanofi and Genentech; research support from Biogen Idec, Teva Neuroscience, EMD Serono, Novartis, Genzyme , Sanofi, Genentech and Mallinckrodt Pharmaceuticals, Inc; serves as an editorial board member for BMJ Neurology, Journal of International MS and CNS Drugs. Dr. Zabeti has received speaking fees from Acorda, Biogen, and Genzyme/Sanofi; research support from Actelion, Genentech/Roche, Novartis, and Opera. Drs. Apperson, Bashir, Conw it, Debbins, Delgado, Giesser, Jubelt, Lava, Nakamura, Narayanan, Natarajan, Perumal, Sakaie, Shinnar, Suski, Yadav, and Zhou, Mr. Gleason, and Yankey, Ms. Ashokkumar, Ecklund, Huang, Klinger, Koepp, McGovern, and Thornell report no disclosures.

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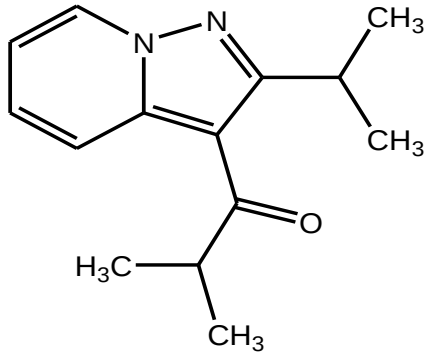
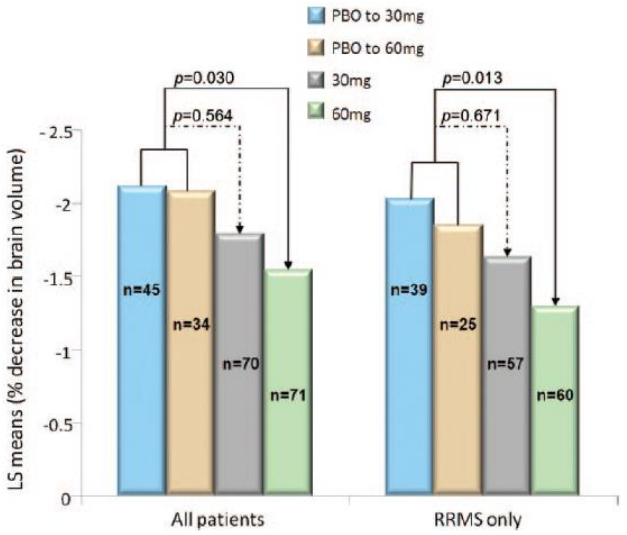
Ibudilast (MN-166, AV411)

- Orally-available small molecule
  - Macrophage migration inhibitor factor (MIF) inhibitor
  - Phosphodiesterase(PDE)-4 and PDE-10 inhibitor
  - Toll-like receptor 4 inhibitor
- Approved in Japan in 1989
  - Bronchial asthma
  - Post-stroke dizziness
- Reduces atrophy progression and black hole formation in RRMS
- Animal models suggest neuroprotection:
  - Krabbe's disease
  - Spinal cord injury
  - Traumatic brain injury
  - Chronic neuropathic pain
  - Cerebral aneurysm





Barkhof et al, Neurol 2010

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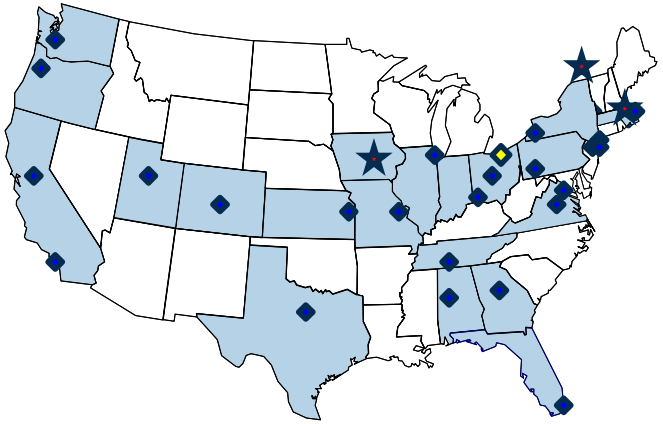
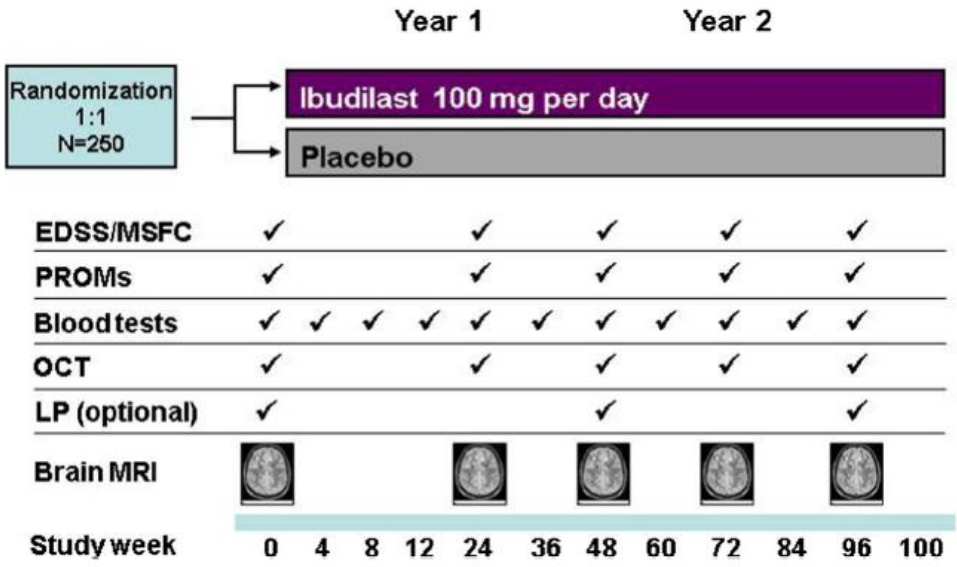
Study Overview





- 28-site, phase II trial
- NIH-sponsored NeuroNEXT network
- 3T MRIs – GE, Siemens

- Inclusion:
  - Age 18-65 years
  - PPMS or SPMS
  - Typical MS lesions on brain MRI (Swanton's Criteria)
  - EDSS 3.0-6.5
  - Disability progression in the preceding 2 years (EDSS, 25FW, 9HPT)
  - Concurrent treatment with IFN or GA allowed
- Exclusion:
  - Current use of any other DMT

Fox et al, Contemporary Clin Trials, 2016

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Study Endpoints

- Primary:
  - Brain atrophy – Brain Parenchymal Fraction (BPF)
  - Safety – AEs, SAEs
  - Tolerability – early discontinuation

- Secondary
  - Magnetization Transfer Ratio – normal-appearing tissue
  - Diffusion Tensor Imaging – descending pyramidal tracts
  - Optical Coherence Tomography - retinal nerve fiber layer
  - Cortical atrophy - Cortical Longitudinal Atrophy Detection Algorithm

Fox et al, Contemporary Clin Trials, 2016

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Fox et al, Contemporary Clin Trials, 2016

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Design and Analysis

- 1:1 Randomization
  - Ibudilast (60, 80, or 100mg/d, as tolerated)
  - Matching placebo
  - Stratified by disease (PPMS/SPMS) and DMT (untreated or on IFN/GA)
- Modified Intent-to-Treat
  - Randomized, received ≥1 dose study medication, ≥1 MRI efficacy assessment
  - Sensitivity analysis: per-protocol population
- Analysis:
  - Linear mixed effect model (MRI)
  - Logistic regression model or Fisher's Exact test (safety and tolerability)
  - Alpha: 0.1

Fox et al, Contemporary Clin Trials, 2016

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Baseline characteristics

	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 (yrs)	**11.7 (9.0)**	**12.2 (9.3)**	**0.65**
EDSS	**5.38 (1.09)**	**5.43 (1.09)**	**0.74**
On DMT (IFN or GA)	40 (32%)	40 (31%)	0.90
BPF	**0.80 (0.0295)**	**0.80 (0.0298)**	**0.75**
DTI - LD (Left)	1.24 (0.049)	1.25 (0.057)	0.23
DTI - LD (Right)	1.24 (0.057)	1.25 (0.062)	0.14
DTI - TD (Left)	0.56 (0.045)	0.55 (0.040)	0.054
DTI - TD (Right)	0.56 (0.045)	0.54 (0.042)	0.042
MTR – NABT	0.31 (0.31)	0.29 (0.25)	0.58
MTR – NAGM	-0.28 (0.30)	-0.31 (0.23)	0.35

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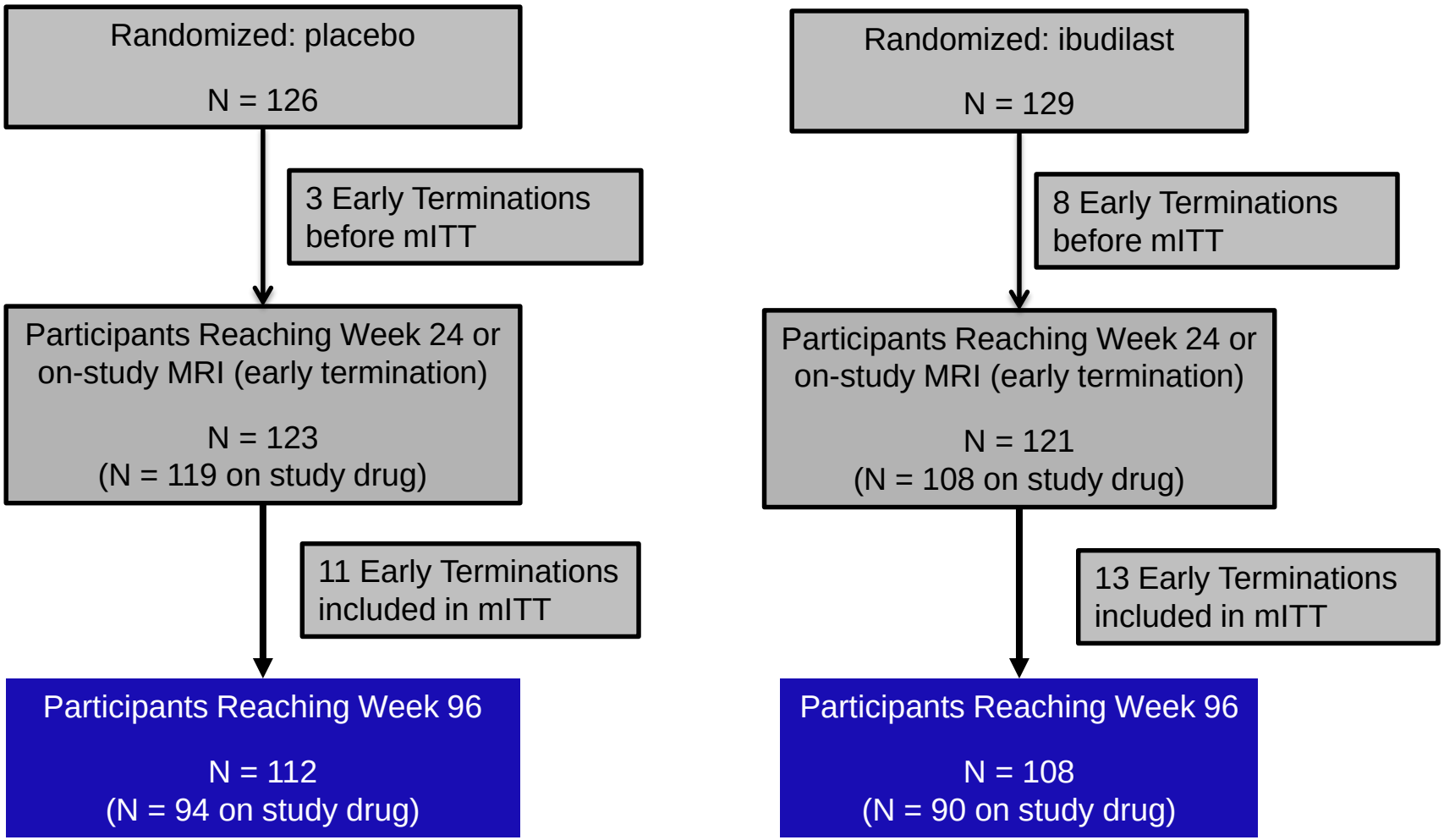
Participant Disposition



86% overall retention rate through Week 96

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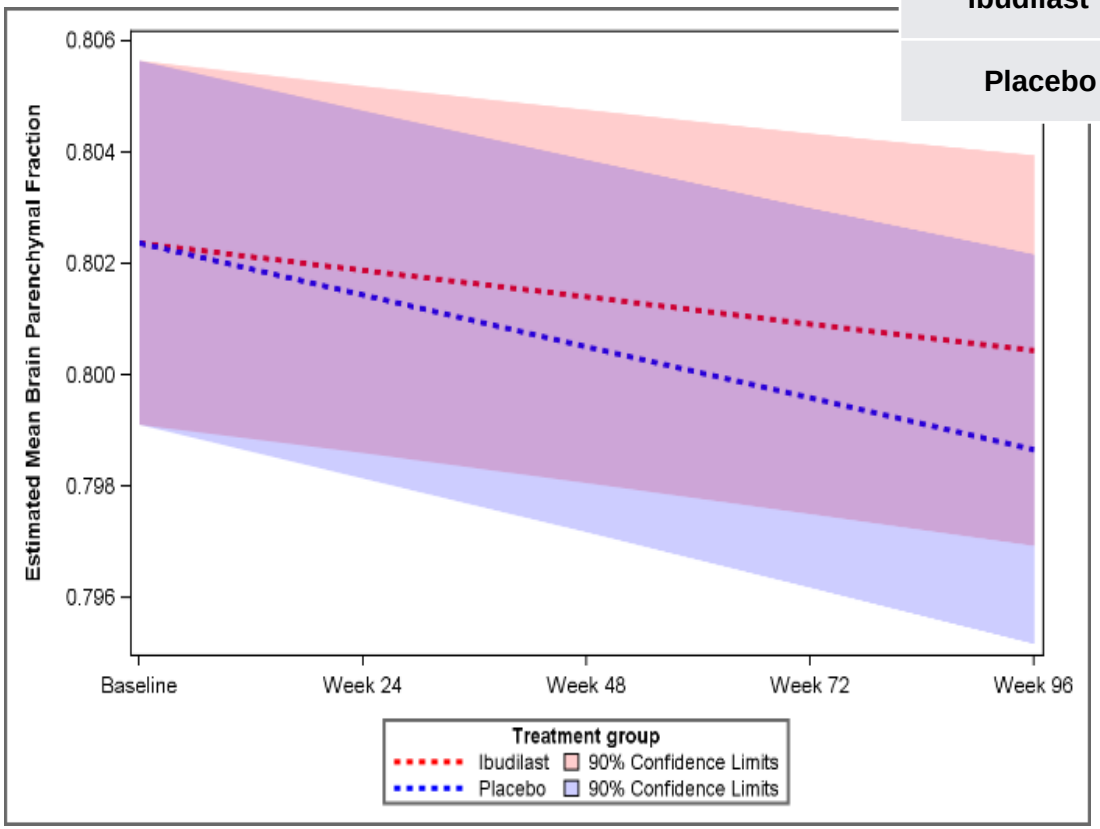
Primary Objective 1: BPF

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)**	



Primary results show significant difference in slope of BPF over time.

Treatment with ibudilast was associated with a 48% slowing in rate of decline.

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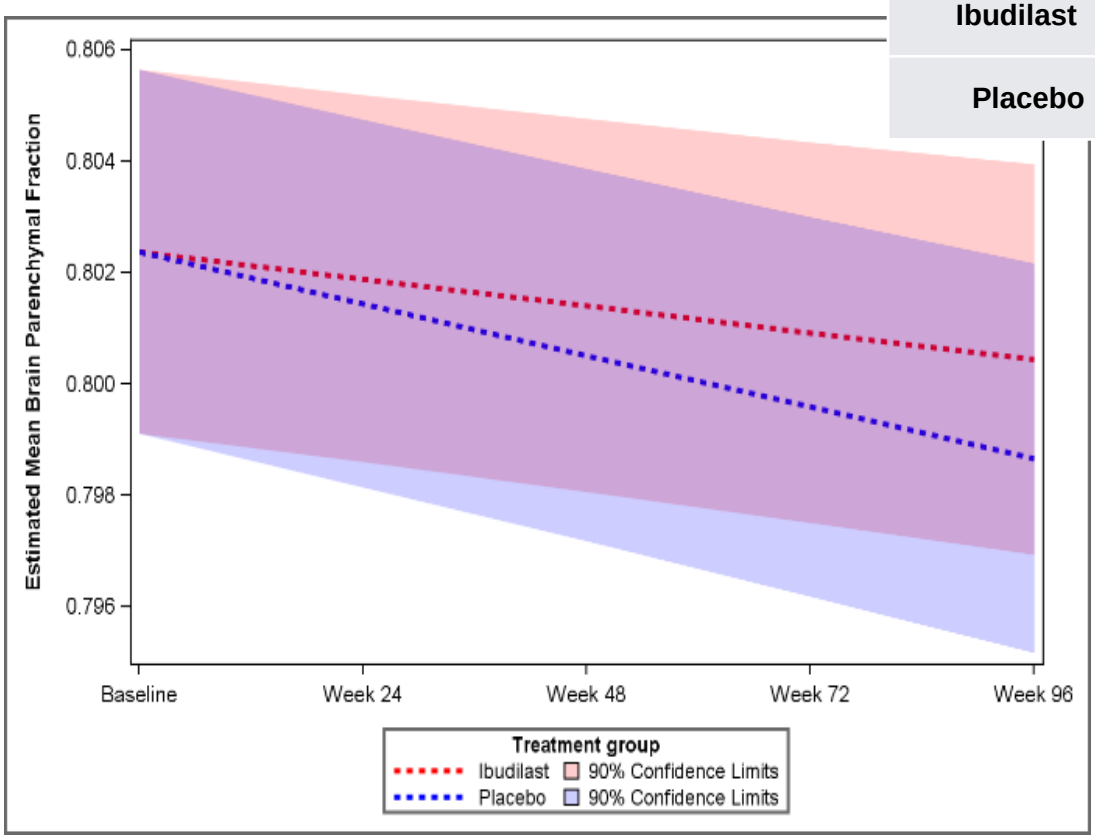
Primary Objective 1: BPF

Per Protocol Analysis:

Estimated Rate of Annual BPF Change		
Treatment Group	**Estimate (90% CI)**	**P-Value**
Ibudilast	**-0.00101 (-0.00159, -0.00043)**	**0.045**
Placebo	**-0.00200 (-0.00258, -0.00143)**	



Results of sensitivity analysis are consistent with findings from primary analysis.

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Primary Objective 2: Safety

Treatment Emergent Adverse Events:

	Placebo	Ibudilast	p-value
Any Adverse Event	**88%**	**92%**	**0.26**
Gastrointestinal System Organ Class	39%	51%	0.050
- Nausea	15%	27%	0.020
- Diarrhoea	7%	16%	0.027
- Abdominal Pain	0%	5%	0.030
- Abdominal Pain, Upper	0%	4%	0.060
- Vomiting	2%	7%	0.098
Other			
- Depression (Psychiatric)	3%	9%	0.048
- Upper Respiratory Tract Infection (Infections)	19%	10%	0.045
- Neck Pain (Musculoskeletal)	3%	0%	0.058
- Skin Infection (Infections)	6%	1%	0.062

AEs with a group difference of $p<0.1$

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Primary Objective 2: Safety

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 (General)	1%	5%	0.096
- Atrioventricular Block First Degree (Cardiac)	3%	0%	0.058
- Neck Pain (Musculoskeletal)	3%	0%	0.058
- Skin Infection (Infections)	6%	1%	0.062

AEs with a group difference of $p<0.1$ SOC – System Organ Class

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Primary Objective 2: Safety

Serious Adverse Events – 58 SAEs (in 44 participants)

Assessment by Independent Medical Monitor

- 2 Related & Anticipated
  - 1 Placebo (Thrombocytopenia)
  - 1 Ibudilast (Ataxia)
- 0 Related & Unanticipated
- 22 Not Related & Unanticipated:

10 Ibudilast:

Nephrolithiasis x 2
Cervical Carcinoma Stage 0
Clostridium Difficile
Febrile Neutropenia
Fracture
Hypercalcaemia
Myocardial Infarction
Pain
Rotator Cuff Syndrome

12 Placebo:

Atrial Fibrillation
Bladder Transitional Cell Carcinoma
Breast Cancer
Cerebrovascular Accident
Choleothiasis
Colonic Obstruction
Endometrial Cancer
Forearm Fracture
Gastroenteritis
Injury
Intestinal Obstruction
Sepsis

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- 22 Not Related & Unanticipated:

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12 Placebo:
Atrial Fibrillation
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Breast Cancer
Cerebrovascular Accident
Choleothiasis
Colonic Obstruction
Endometrial Cancer
Forearm Fracture
Gastroenteritis
Injury
Intestinal Obstruction
Sepsis

- No reports of suicidality or suicidal attempts

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Primary Objective 2: Tolerability

	Placebo	Ibudilast	p-value
Discontinue Treatment			
- Any Reason	25%	30%	0.39
- Due to AE	12%	18%	0.18
Early Study Terminations			
- Any Reason	11%	16%	0.28
- Due to AE	4%	8%	0.29
Early Drug Withdrawal			
- Any Reason	16%	18%	0.74
- Due to AE	9%	12%	0.42

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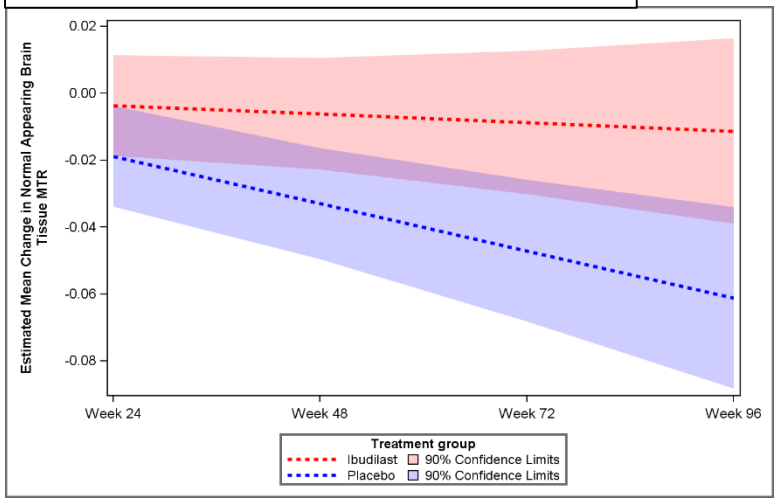
Major Secondary Objective: MTR

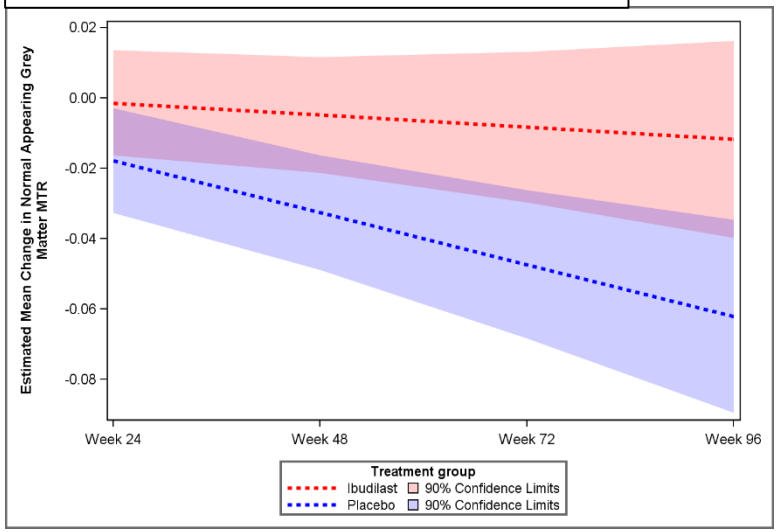
Normal-appearing Brain Tissue



Estimated Rate of Change Per 1 Yr		
Treatment Group	**Estimate (90% CI)**	**P-Value**
Ibudilast	**-0.00558 (-0.02297, 0.01181)**	**0.047**
Placebo	**-0.03064 (-0.04767, -0.01362)**	

Significant difference in slope in both MTR measures.

Normal-appearing Gray Matter



Treatment with ibudilast was associated with an 77-82% slowing in rate of MTR decline.

Estimated Rate of Change Per 1 Yr		
Treatment Group	**Estimate (90% CI)**	**P-Value**
Ibudilast	**-0.00753 (-0.02565, 0.01059)**	**0.054**
Placebo	**-0.03210 (-0.04988, -0.01433)**	

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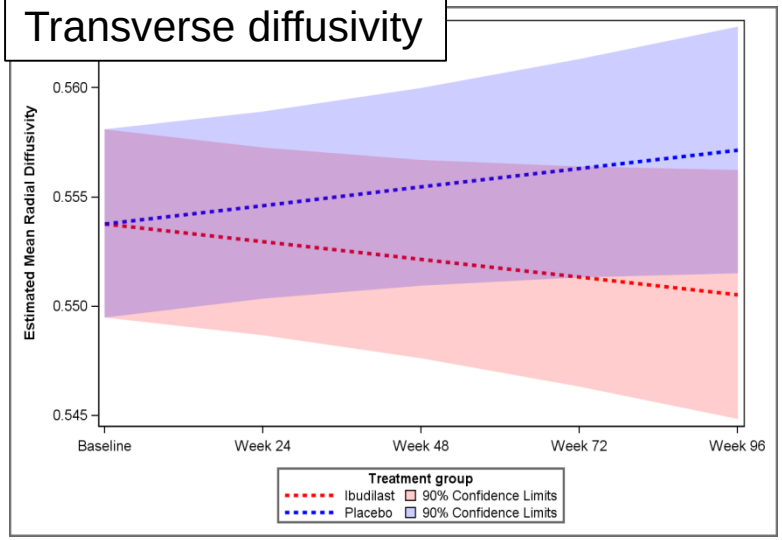
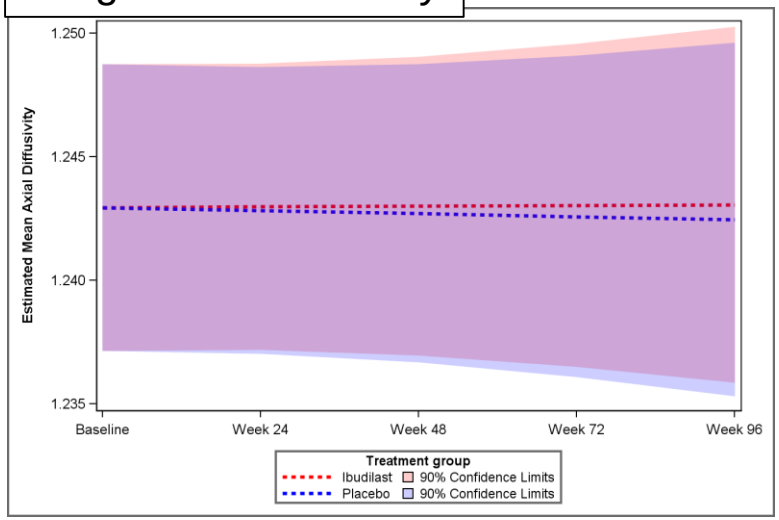
Major Secondary Objective: DTI

Transverse diffusivity



Estimated Rate of Change Per 1 Yr		
Treatment Group	Estimate (90% CI)	P-Value
Ibudilast	-0.00157 (-0.00417, 0.00102)	0.15
Placebo	0.00160 (-0.00096, 0.00416)	

Longitudinal diffusivity



Estimated Rate of Change Per 1 Yr		
Treatment Group	Estimate (90% CI)	P-Value
Ibudilast	0.00009 (-0.00285, 0.00303)	0.73
Placebo	-0.00076 (-0.00367, 0.00214)	

No significant difference observed in either DTI measure.

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Overall 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
  - ~5% higher discontinuation rate in ibudilast group

Analysis of OCT, cortical atrophy, and clinical outcomes is underway, as well as additional safety and laboratory analyses.

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