# A Phase II Trial of Ibudilast in Progressive Multiple Sclerosis



R.J. Fox, C.S. Coffey, M.E. Cudkowicz, T. Gleason, A. Goodman, E.C. Klawiter, K. Matsuda, M. McGovern, R. Conwit, R. Naismith, A. Ashokkumar, J. Barnes, D. Ecklund, E. Klinger, M. Koepp, S. Natarajan, B. Thornell, J. Yankey, R.A. Bermel, X. Huang, M.J. Lowe, K. Nakamura, S. Narayanan, K.E. Sakaie, J.P. Debbins, X. Zhou, E. Alvarez, M. Apperson, K. Bashir, B. Cohen, P. Coyle, S. Delgado, D. Dewitt, A. Flores, B. Giesser, M. Goldman, B. Jubelt, N. Lava, S. Lynch, H. Moses, D. Ontaneda, J. Perumal, M. Racke, P. Repovic, C. Riley, C. Severson, S. Shinnar, V. Suski, B. Weinstock-Guttman, V. Yadav, A. Zabeti, on behalf of the NN102/SPRINT-MS Investigators





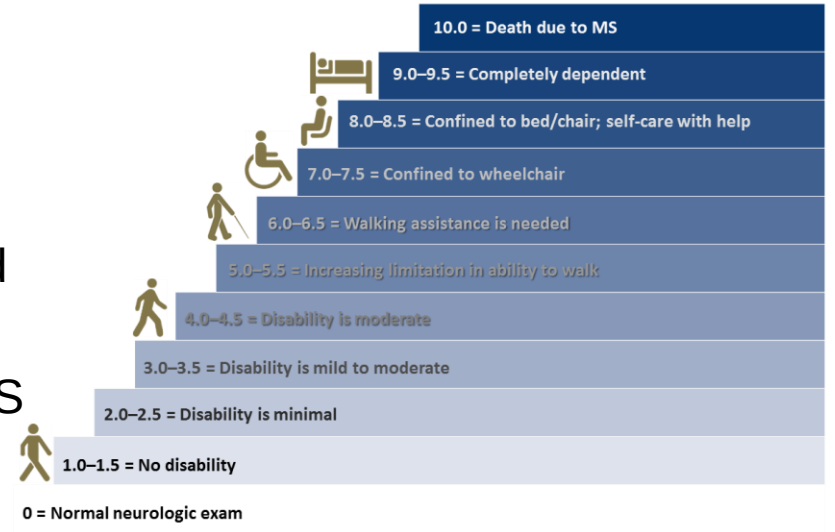

# Disclosures

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. Cudkowicz 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.

SPRINT-MS

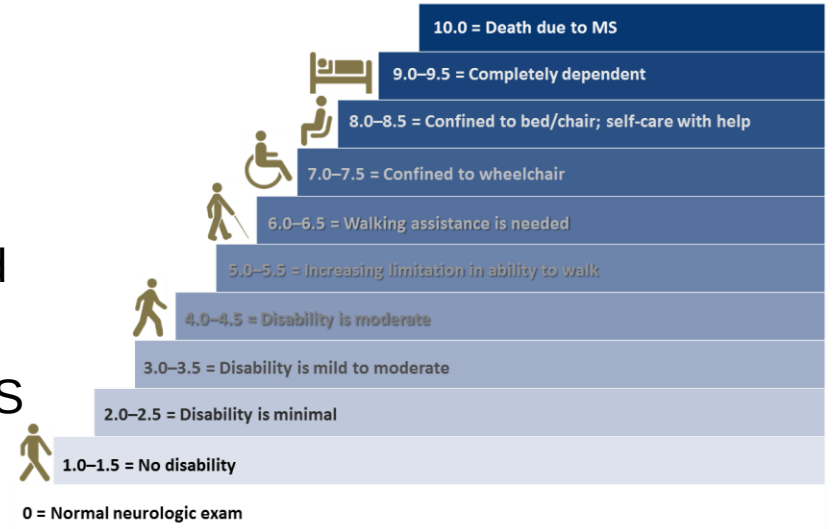
# Progressive Multiple Sclerosis

- About half of people living with multiple sclerosis have progressive MS (primary and secondary progressive)
  - Manifests as gradual decline in neurologic function
  - Primary and secondary progressive MS are increasingly recognized as having more similarities than differences
- There are limited therapies with demonstrated efficacy in progressive MS
- Ideally, a new therapy can be added to other MS therapies

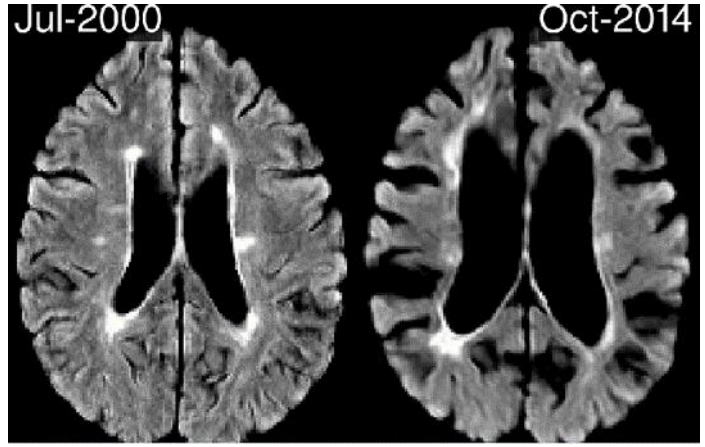


# Progressive Multiple Sclerosis

- About half of people living with multiple sclerosis have progressive MS (primary and secondary progressive)
  - Manifests as gradual decline in neurologic function
  - Primary and secondary progressive MS are increasingly recognized as having more similarities than differences
- There are limited therapies with demonstrated efficacy in progressive MS
- Ideally, a new therapy can be added to other MS therapies




- Biomarkers for Phase II proof-of-concept clinical trials have only partial validation
  - Whole brain atrophy is more widely used outcome
    - Is limited to a single value per brain – lacks granularity
  - Better phase 2 trial outcome markers could make trials more efficient
- Ideally, a Phase 2 trial in progressive MS will compare biomarkers

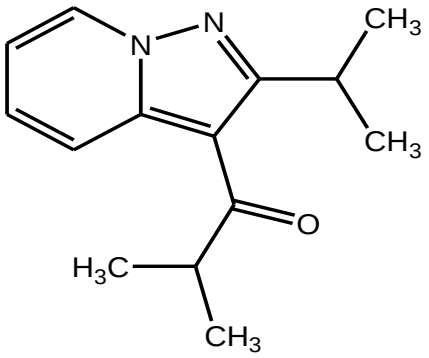


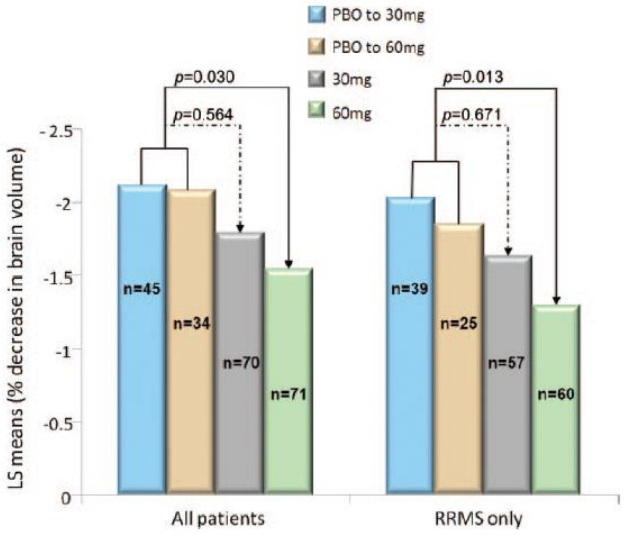

Nakamura et al, in preparation

SPRINT-MS

# Ibudilast (MN-166, AV411)

- Orally-available small molecule
  - Phosphodiesterase PDE-4 and PDE-10 inhibitor
  - Macrophage migration inhibitor factor inhibitor
  - Toll-like receptor 4 inhibitor
- Approved in Japan in 1989
  - Bronchial asthma
  - Post-stroke dizziness
- Slowed progression of atrophy and reduces black hole formation in relapsing MS, although mechanism of action in MS is unknown
- Animal models suggest neuroprotection:
  - Krabbe's disease
  - Spinal cord injury
  - Traumatic brain injury
  - Chronic neuropathic pain
  - Cerebral aneurysm

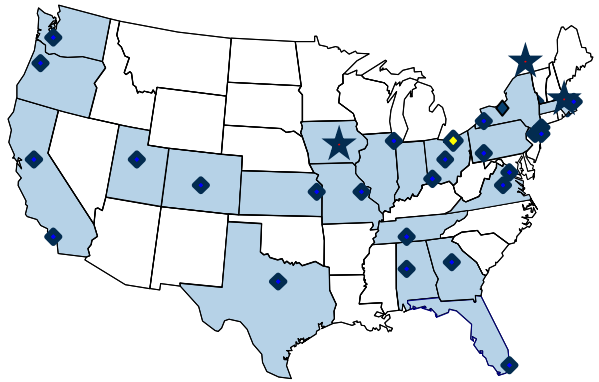


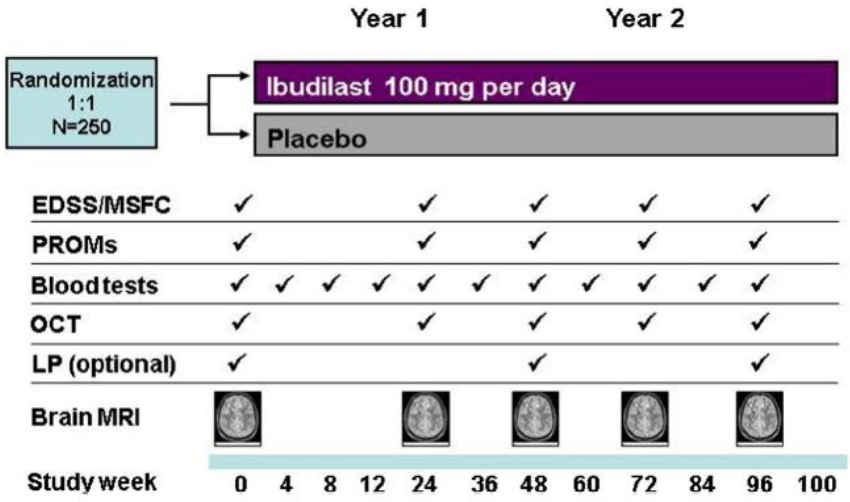




Barkhof et al, Neurol 2010

SPRINT-MS

# NN102 / SPRINT-MS Trial Overview






- 96-week, 28-site, phase II trial utilizing NIH-sponsored NeuroNEXT network
- Inclusion:
  - Age 18-65 years
  - Primary or secondary progressive MS
  - Typical MS lesions on brain MRI
  - Expanded Disability Status Scale 3.0-6.5
  - Disability progression in the preceding 2 years (EDSS, 25FW, 9HPT)
  - Concurrent treatment with IFN or GA allowed
- Imaging
  - 3T MRIs – GE, Siemens
  - Spectral domain optical coherence tomography
- 1:1 Randomization to ibudilast or matching placebo
  - Stratified by disease (PPMS/SPMS) and DMT (untreated or IFN/GA)
- Modified intent-to-treat analysis
  - Randomized, received study medication, ≥1 MRI efficacy assessment
- Analysis
  - Linear mixed effect model (imaging outcomes)
  - Logistic regression model or Fisher's Exact test (safety and tolerability)
  - Alpha: 0.1

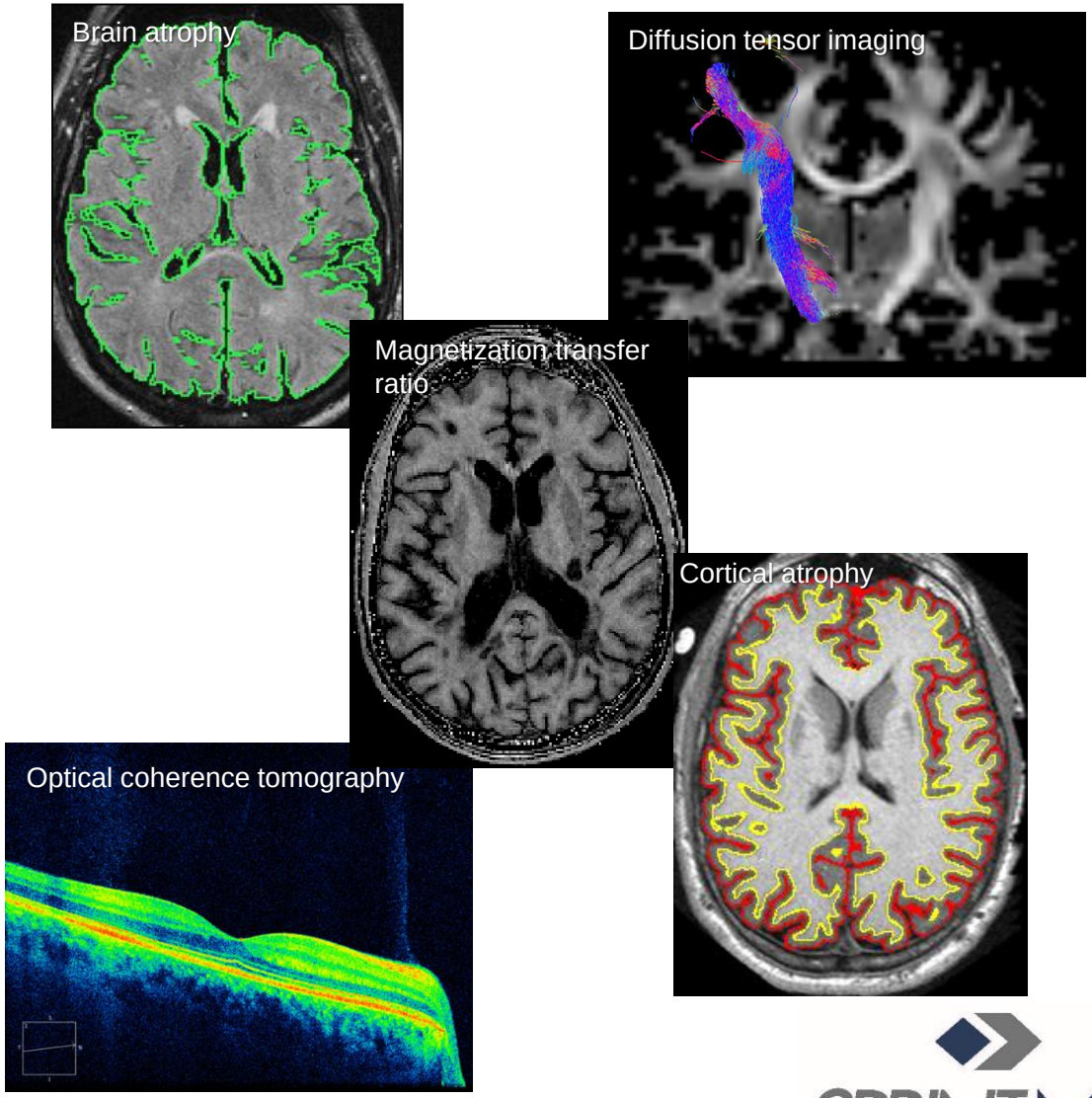
Fox et al, Contemporary Clin Trials, 2016

SPRINT-MS

# Study Endpoints

- Primary:
  - Whole brain atrophy – Brain Parenchymal Fraction (BPF)
  - Safety – Adverse events, Serious adverse events
  - Tolerability – early discontinuation

- Secondary
  - Diffusion Tensor Imaging in pyramidal tracts
  - Magnetization Transfer Ratio in normal-appearing brain tissue
  - Retinal Nerve Fiber Layer Thickness - Optical Coherence Tomography
  - Cortical atrophy - Cortical Longitudinal Atrophy Detection Algorithm




Fox et al, Contemporary Clin Trials, 2016

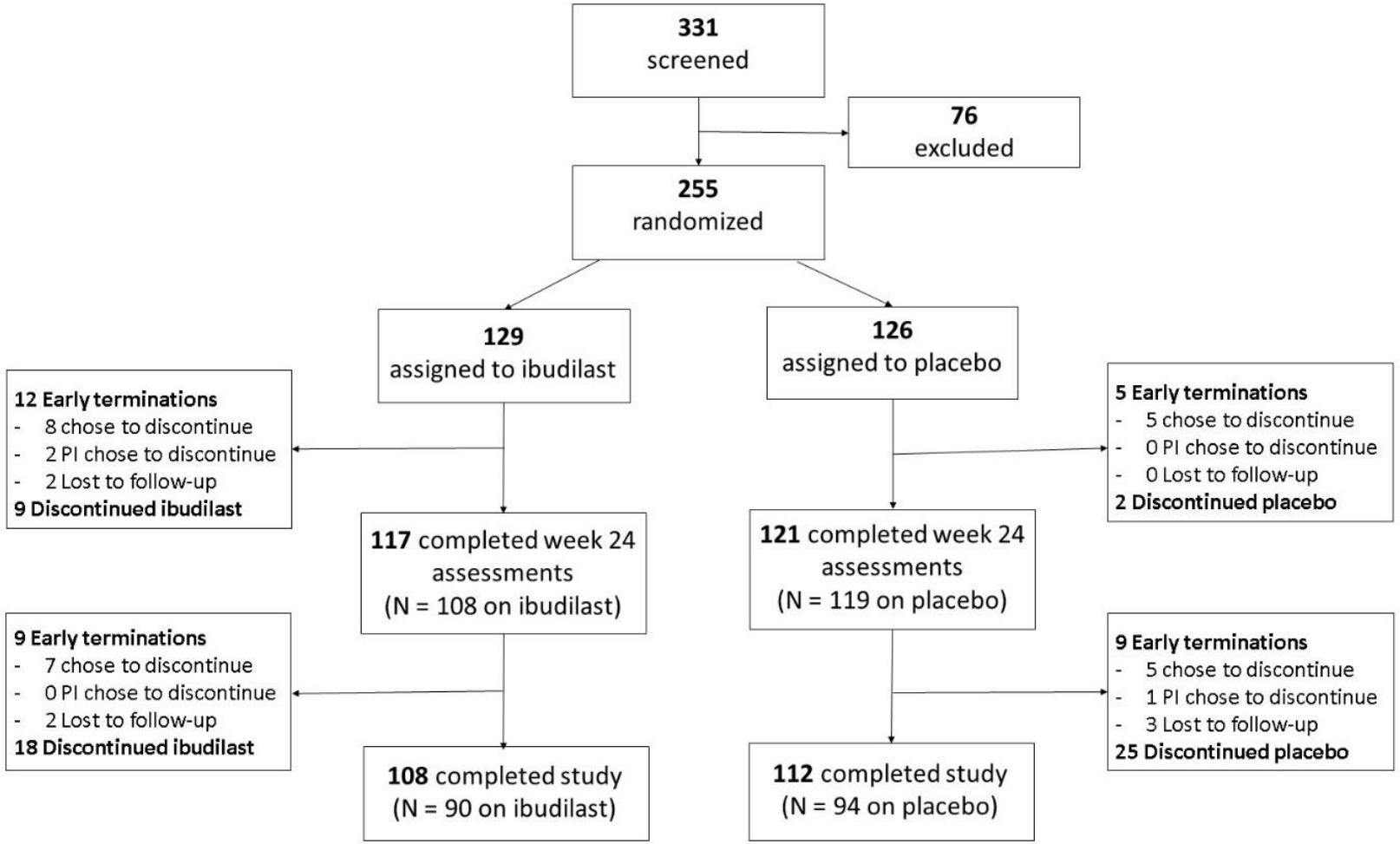
SPRINT-MS

# Baseline characteristics

| | Characteristic | Placebo (n = 126) | Ibudilast (n = 129) | P-value |
|---|---|---|---|---|
| Demographics | Age (yrs), mean (SD) | 57 (6.5) | 55 (7.8) | 0.02 |
| | Females, n (%) | 69 (55%) | 67 (52%) | 0.65 |
| | Race | | | |
| | Caucasian, n (%) | 114 (91%) | 122 (95%) | 0.79 |
| | Black / African American, n (%) | 7 (6%) | 4 (3%) | |
| | Other, n (%) | 1 (1%) | 3 (2%) | |
| | Unknown/Not Reported, n (%) | 4 (3%) | 0 (0%) | |
| | Hispanic/Latino, n (%) | 3 (2%) | 4 (3%) | 1.00 |
| Multiple Sclerosis | Primary Progressive, n (%) | 66 (52%) | 68 (53%) | 0.96 |
| | Use of Injection MS Therapy, n (%) | 40 (32%) | 40 (31%) | 0.90 |
| | Glatiramer Acetate, n (%) | 24 (19%) | 19 (15%) | |
| | Interferon-beta, n (%) | 16 (13%) | 21 (16%) | |
| | Disease Duration (yrs), median (min, max) | 9 (0,36) | 11 (0, 41) | 0.64 |
| | Expanded Disability Status Scale, median (min, max) | 6.0 (3.0, 7.0) | 6.0 (2.5, 6.5) | 0.68 |
| Imaging | Brain parenchymal fraction (unitless), mean (SD) | 0.80 (0.0295) | 0.80 (0.0298) | 0.75 |
| | T2 Lesion volume ($cm^3$), mean (SD) | 10 (11.2) | 10 (11.1) | 0.99 |
| | Magnetization transfer ratio in normal-appearing brain tissue (normalized units), mean (SD) | 0.31 (0.31) | 0.29 (0.25) | 0.58 |
| | Cortical thickness (mm), mean (SD) | 3.03 (0.22) | 3.04 (0.23) | 0.72 |
| | Longitudinal diffusivity ($10^{-3}$ $mm^2$/sec), mean (SD) | 1.24 (0.05) | 1.25 (0.06) | 0.15 |
| | Transverse diffusivity ($10^{-3}$ $mm^2$/sec), mean (SD) | 0.56 (0.04) | 0.55 (0.04) | 0.04 |
| | Retinal nerve fiber layer thickness (µm), mean (SD) | 81.15 (13.15) | 83.15 (10.81) | 0.19 |

SPRINT-MS

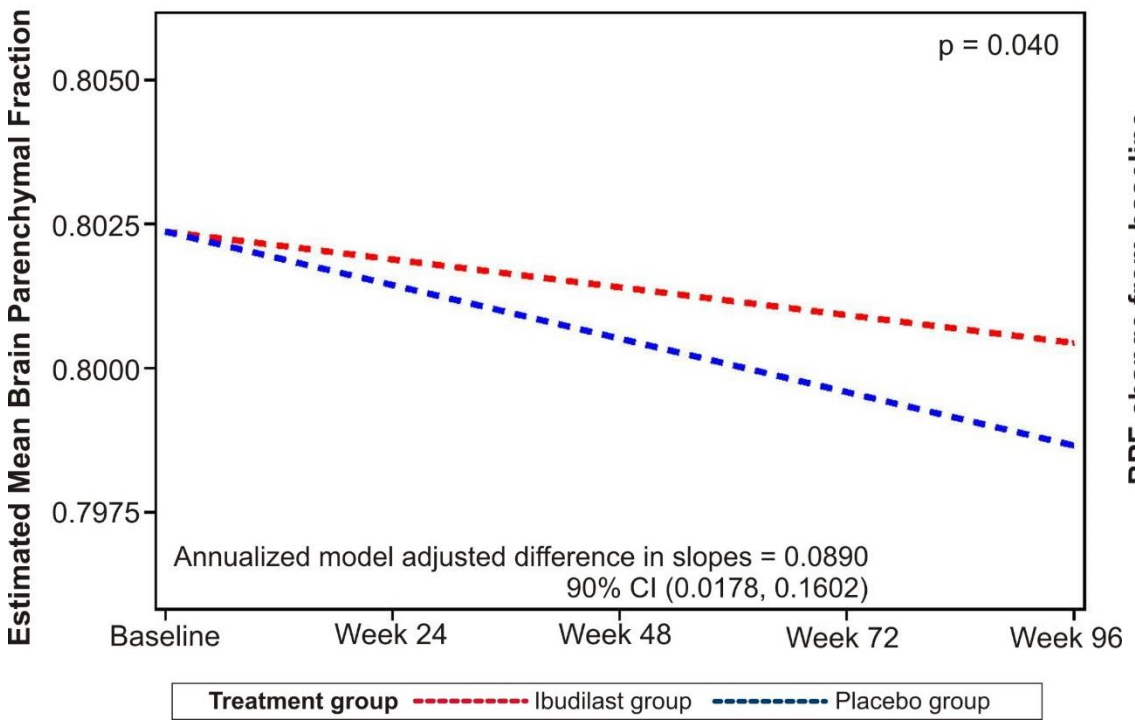
# Participant Disposition

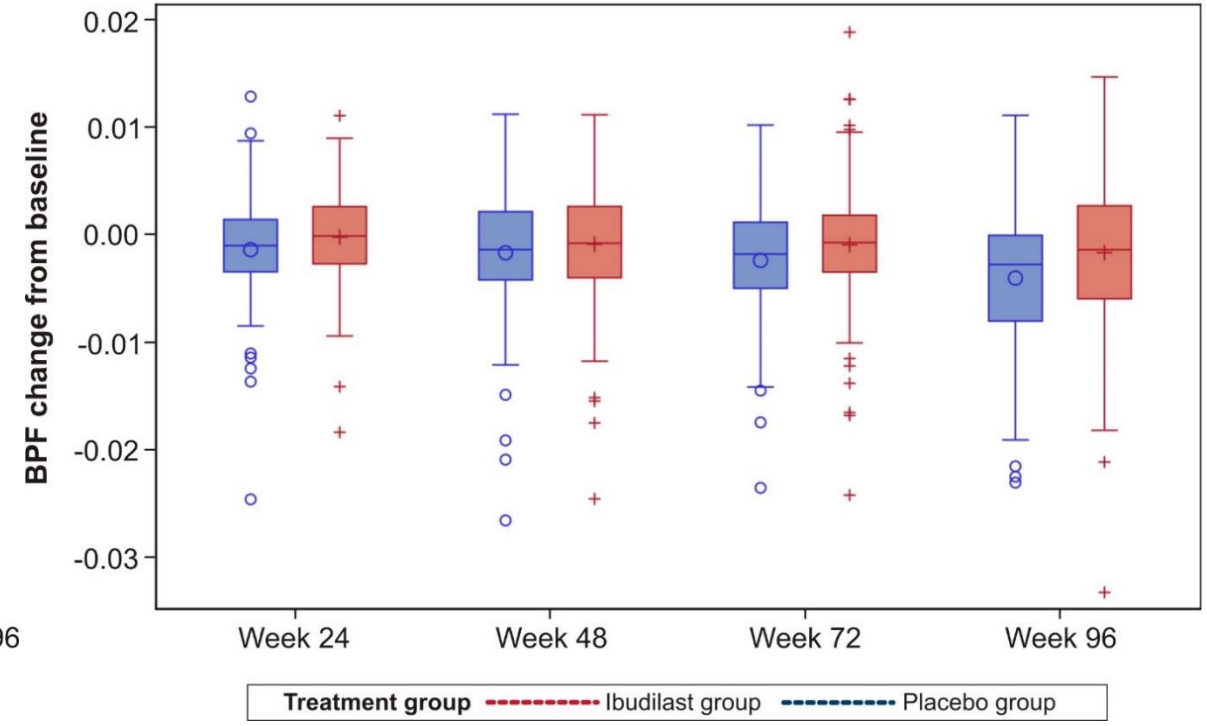



86% overall retention rate through Week 96

SPRINT-MS

# Primary Outcome: Brain Atrophy




Compared to placebo, ibudilast treatment was associated with a 48% slowing in rate of atrophy progression

- There was no evidence for outliers driving the overall result
- A modified per-protocol sensitivity analysis was consistent with findings from the primary analysis (p=0.02)
- Similarly, analysis to adjust for baseline age was consistent (p = 0.03)

SPRINT-MS

# Primary Outcome: Safety and Tolerability

Adverse events more frequent in one group (p≤0.10) or reported in more than ≥10%

| | Overall (N = 255) | Placebo (N = 126) | Ibudilast (N = 129) | P value |
|---|---|---|---|---|
| **All Adverse Events** | 230 (90%) | 111 (88%) | 119 (92%) | 0.26 |
| **Gastrointestinal** | | | | |
| **Abdominal pain** | 6 (2%) | 0 (0%) | 6 (5%)* | 0.03 |
| **Abdominal pain upper** | 5 (2%) | 0 (0%) | 5 (4%)* | 0.06 |
| **Diarrhea** | 30 (12%) | 9 (7%) | 21 (16%)* | 0.03 |
| **Nausea** | 54 (21%) | 19 (15%) | 35 (27%)* | 0.02 |
| **Vomiting** | 12 (5%) | 3 (2%) | 9 (7%)* | 0.10 |
| **General** | | | | |
| **Fatigue** | 25 (10%) | 11 (9%) | 14 (11%) | 0.57 |
| **Infections** | | | | |
| **Skin infection** | 8 (3%) | 7 (6%)* | 1 (1%) | 0.06 |
| **Upper respiratory tract infection** | 37 (15%) | 24 (19%)* | 13 (10%) | 0.05 |
| **Urinary tract infection** | 76 (30%) | 41 (33%) | 35 (27%) | 0.34 |
| **Injury, Poisoning, and Procedural Comp.** | | | | |
| **Fall** | 49 (19%) | 20 (16%) | 29 (23%) | 0.18 |
| **Musculoskeletal** | | | | |
| **Back pain** | 25 (10%) | 15 (12%) | 10 (8%) | 0.27 |
| **Neck pain** | 4 (2%) | 4 (3%)* | 0 (0%) | 0.06 |
| **Pain in extremity** | 18 (7%) | 13 (10%)* | 5 (4%) | 0.05 |
| **Nervous System** | | | | |
| **Headache** | 38 (15%) | 15 (12%) | 23 (18%) † | 0.19 |
| **Psychiatric** | | | | |
| **Depression** | 16 (6%) | 4 (3%) | 12 (9%)* | 0.05 |
| **Insomnia** | 25 (10%) | 11 (9%) | 14 (11%) | 0.57 |

† A higher rate of headaches was observed in ibudilast group (p=0.09)

SPRINT-MS

# Primary Outcome: Safety and Tolerability

Adverse events more frequent in one group (p≤0.10) or reported in more than ≥10%

| | Overall (N = 255) | Placebo (N = 126) | Ibudilast (N = 129) | P value |
|---|---|---|---|---|
| **All Adverse Events** | 230 (90%) | 111 (88%) | 119 (92%) | 0.26 |
| **Gastrointestinal** | | | | |
| **Abdominal pain** | 6 (2%) | 0 (0%) | 6 (5%)* | 0.03 |
| **Abdominal pain upper** | 5 (2%) | 0 (0%) | 5 (4%)* | 0.06 |
| **Diarrhea** | 30 (12%) | 9 (7%) | 21 (16%)* | 0.03 |
| **Nausea** | 54 (21%) | 19 (15%) | 35 (27%)* | 0.02 |
| **Vomiting** | 12 (5%) | 3 (2%) | 9 (7%)* | 0.10 |
| **Nervous System** | | | | |
| **Headache** | 38 (15%) | 15 (12%) | 23 (18%) † | 0.19 |
| **Psychiatric** | | | | |
| **Depression** | 16 (6%) | 4 (3%) | 12 (9%)* | 0.05 |
| **Insomnia** | 25 (10%) | 11 (9%) | 14 (11%) | 0.57 |

† A higher rate of headaches was observed in ibudilast group (p=0.09)

SPRINT-MS

# Primary Outcome: Safety and Tolerability

Adverse events more frequent in one group (p≤0.10) or reported in more than ≥10%

| | Overall (N = 255) | Placebo (N = 126) | Ibudilast (N = 129) | P value |
|---|---|---|---|---|
| **All Adverse Events** | 230 (90%) | 111 (88%) | 119 (92%) | 0.26 |
| **Gastrointestinal** | | | | |
| **Abdominal pain** | 6 (2%) | 0 (0%) | 6 (5%)* | 0.03 |
| **Abdominal pain upper** | 5 (2%) | 0 (0%) | 5 (4%)* | 0.06 |
| **Diarrhea** | 30 (12%) | 9 (7%) | 21 (16%)* | 0.03 |
| **Nausea** | 54 (21%) | 19 (15%) | 35 (27%)* | 0.02 |
| **Vomiting** | 12 (5%) | 3 (2%) | 9 (7%)* | 0.10 |
| **General** | | | | |
| **Infections** | | | | |
| **Skin infection** | 8 (3%) | 7 (6%)* | 1 (1%) | 0.06 |
| **Upper resp. tract infection** | 37 (15%) | 24 (19%)* | 13 (10%) | 0.05 |
| **Musculoskeletal** | | | | |
| **Back pain** | 25 (10%) | 15 (12%) | 10 (8%) | 0.27 |
| **Neck pain** | 4 (2%) | 4 (3%)* | 0 (0%) | 0.06 |
| **Pain in extremity** | 18 (7%) | 13 (10%)* | 5 (4%) | 0.05 |
| **Depression** | 16 (6%) | 4 (3%) | 12 (9%)* | 0.05 |
| **Insomnia** | 25 (10%) | 11 (9%) | 14 (11%) | 0.57 |

† A higher rate of headaches was observed in ibudilast group (p=0.09)

SPRINT-MS

# Primary Outcome: Safety and Tolerability

Adverse events more frequent in one group (p≤0.10) or reported in more than ≥10%

| | Overall (N = 255) | Placebo (N = 126) | Ibudilast (N = 129) | P value |
|---|---|---|---|---|
| **All Adverse Events** | 230 (90%) | 111 (88%) | 119 (92%) | 0.26 |
| **Gastrointestinal** | | | | |
| **Abdominal pain** | 6 (2%) | 0 (0%) | 6 (5%)* | 0.03 |
| **Abdominal pain upper** | 5 (2%) | 0 (0%) | 5 (4%)* | 0.06 |
| **Diarrhea** | 30 (12%) | 9 (7%) | 21 (16%)* | 0.03 |
| **Nausea** | 54 (21%) | 19 (15%) | 35 (27%)* | 0.02 |
| **Vomiting** | 12 (5%) | 3 (2%) | 9 (7%)* | 0.10 |
| **General** | | | | |
| **Fatigue** | 25 (10%) | 11 (9%) | 14 (11%) | 0.57 |
| **Infections** | | | | |
| **Skin infection** | 8 (3%) | 7 (6%)* | 1 (1%) | 0.06 |
| **Upper respiratory tract infection** | 37 (15%) | 24 (19%)* | 13 (10%) | 0.05 |
| **Urinary tract infection** | 76 (30%) | 41 (33%) | 35 (27%) | 0.34 |
| **Injury, Poisoning, and Procedural Comp.** | | | | |
| **Fall** | 49 (19%) | 20 (16%) | 29 (23%) | 0.18 |
| **Musculoskeletal** | | | | |
| **Back pain** | 25 (10%) | 15 (12%) | 10 (8%) | 0.27 |
| **Neck pain** | 4 (2%) | 4 (3%)* | 0 (0%) | 0.06 |
| **Pain in extremity** | 18 (7%) | 13 (10%)* | 5 (4%) | 0.05 |
| **Nervous System** | | | | |
| **Headache** | 38 (15%) | 15 (12%) | 23 (18%) † | 0.19 |
| **Psychiatric** | | | | |

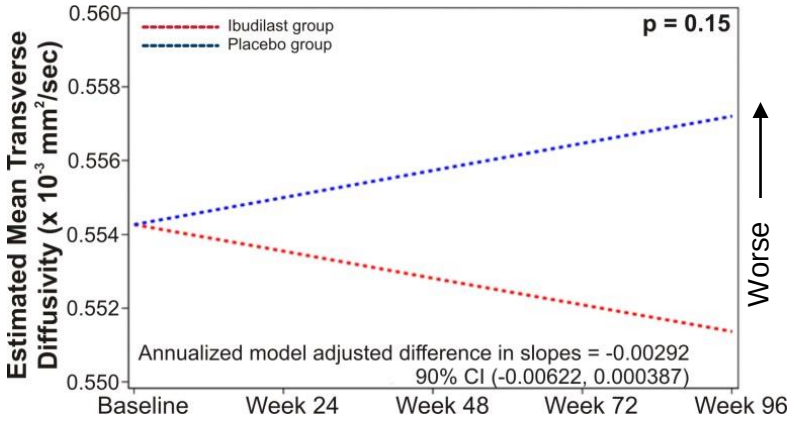
| | Overall | Placebo | Ibudilast | P value |
|---|---|---|---|---|
| **Tolerability** | | | | |
| **Early Termination Due to Any Reason** | 35 (14%) | 14 (11%) | 21 (16%) | 0.24 |
| **Early Termination Due to Adverse Event** | 15 (6%) | 5 (4%) | 10 (8%) | 0.21 |

| | Overall | Placebo | Ibudilast | P value |
|---|---|---|---|---|
| **All Serious Adverse Events** | 44 (17%) | 24 (19%) Subjects | 20 (16%) Subjects | 0.46 |
| | | Atrial Fibrillation | Asthenia | |
| | | Back pain | Ataxia | |
| | | Bladder Prolapse | Back Pain | |
| | | Bladder Transitional Cell Carcinoma | Cerebral Hemorrhage | |
| | | Breast Cancer | Cervical Carcinoma Stage 0 | |
| | | Cerebrovascular Accident | Clostridium Difficile Colitis | |
| | | Cervical Spinal Stenosis | Dehydration (2) | |
| | | Choleothiasis | Febrile Neutropenia | |
| | | Colonic Obstruction | Fracture | |
| | | Convulsion | Hypercalcemia | |
| | | Cystitis | Hyperkalemia | |
| | | Endometrial Cancer | Metastatic Malignant Melanoma | |
| | | Forearm Fracture | Multiple Fractures | |
| | | Gastroenteritis | Myocardial Infarction | |
| | | Hyponatremia | Nephrolithiasis (2) | |
| | | Injury | Pain | |
| | | Intestinal Obstruction | Pain in extremity | |
| | | Kidney Infection | Rotator Cuff Syndrome | |
| | | Muscular Weakness | Sepsis (2) | |
| | | Parotidectomy | Sinus Tachycardia | |
| | | Pneumonia Aspiration | Spondylitic Myopathy | |
| | | Pulmonary Embolism | Transient Acantholytic Dermotosis | |
| | | Pyrexia | Urinary Tract Infection (2) | |
| | | Sepsis (2) | | |
| | | Skin Infection (2) | | |
| | | Thrombocytopenia | | |
| | | Tooth Infection | | |
| | | Urinary Tract Infection (2) | | |

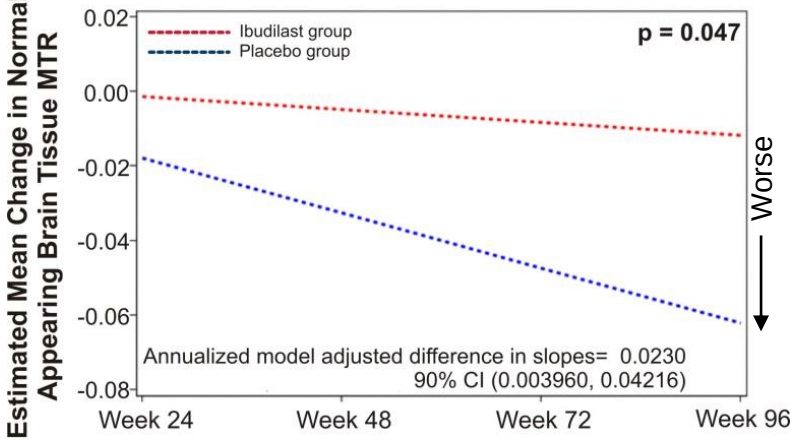
SPRINT-MS

# Key Secondary Outcomes

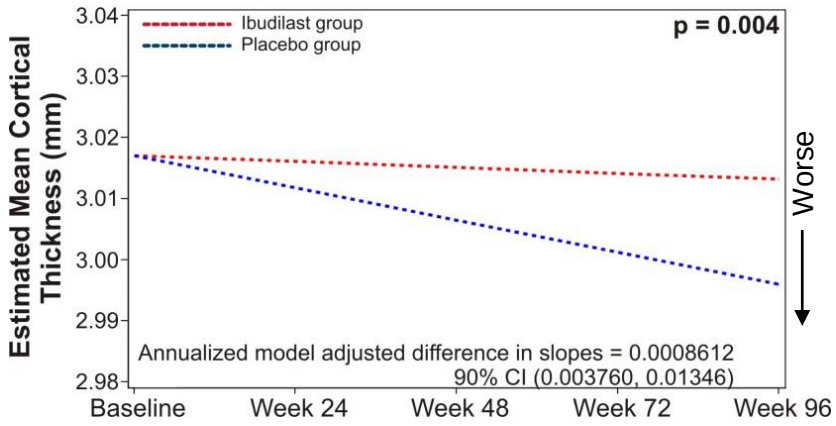
*Change in transverse diffusivity in pyramidal tract*



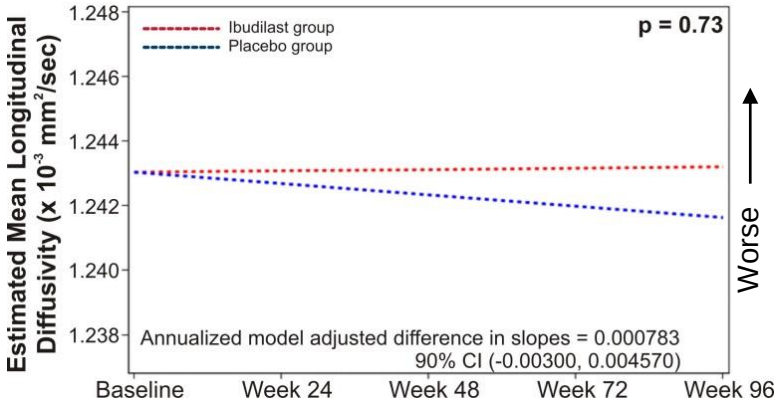

*Change in magnetization transfer ratio in normal-appearing brain tissue*



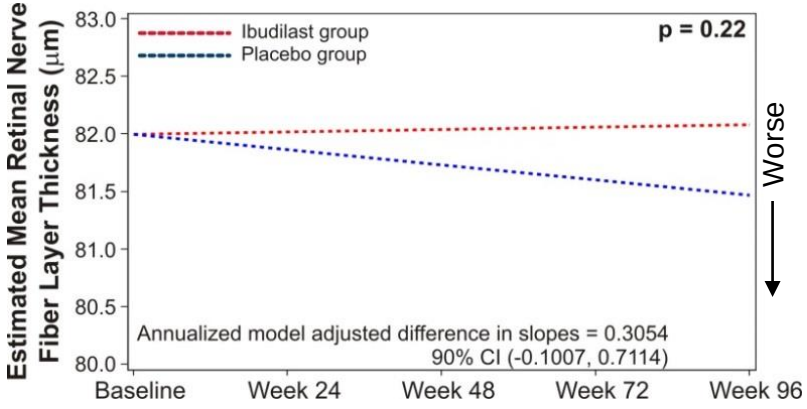

*Change in cortical thickness*




*Change in longitudinal diffusivity in pyramidal tract*




*Change in retinal nerve fiber layer thickness*




Ibudilast was associated with:

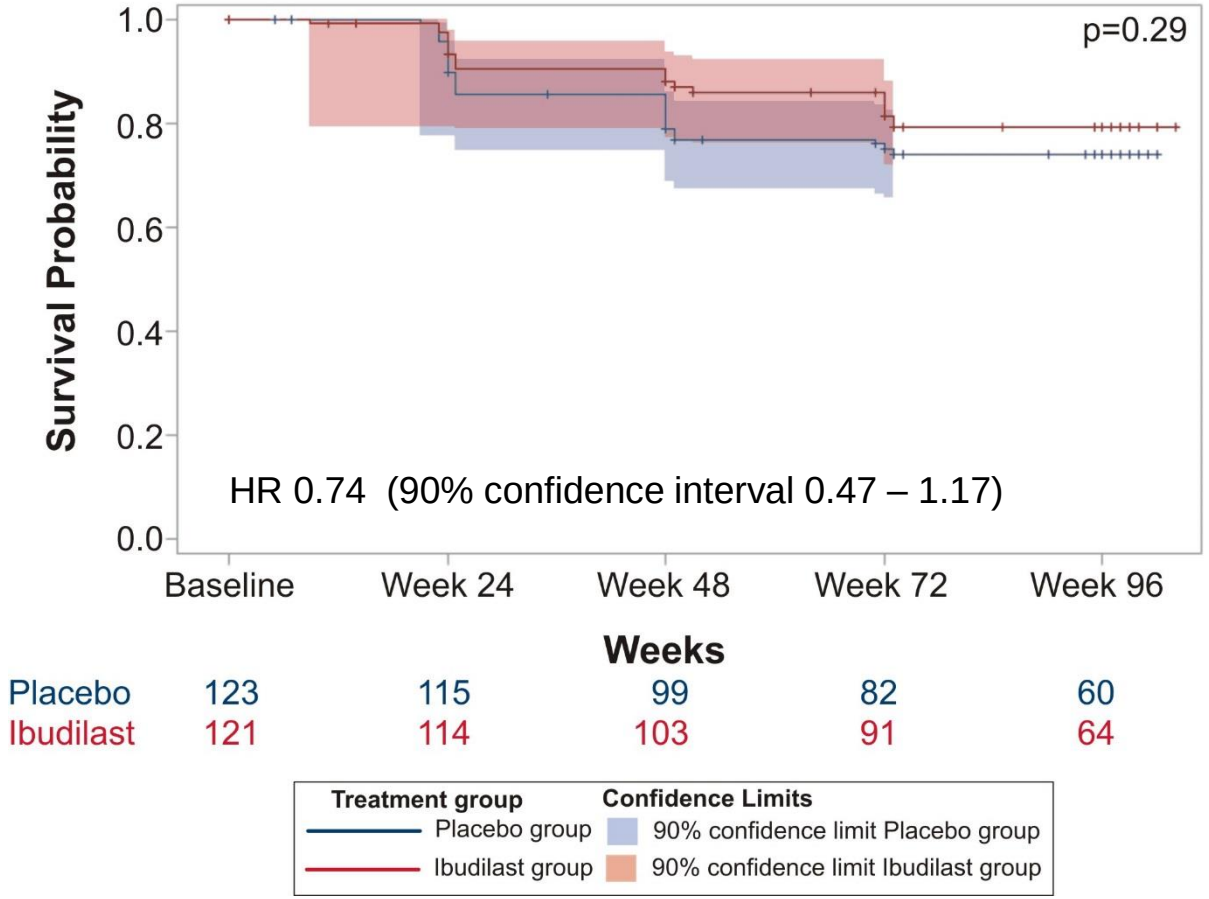
- No effect on progression of diffusion
- 81% slowing in progression of MTR
- No effect on progression of retinal nerve fiber layer thinning
- 80% slowing in progression of cortical atrophy

The clinical relevance of changes in these imaging measures is unknown

SPRINT-MS

# Secondary Outcome - Disability

Sustained progression on Expanded Disability Status Scale




- Progression of disability changed in a favorable direction with ibudilast but was not statistically significant
- This phase 2 trial was not powered to detect benefit on clinical disability

SPRINT-MS

# Overall Conclusions

- Ibudilast treatment led to a 48% slowing in the progression of whole brain atrophy in progressive MS
  - Benefit was also seen with magnetization transfer ratio (81% reduction) and cortical atrophy (80% reduction), but not with diffusion tensor imaging or retinal nerve fiber layer thickness
  - The clinical relevance of these imaging effects is unknown
- Adverse events with ibudilast were gastrointestinal, depression, and headache
- No increased rate of serious adverse events
- No statistically significant difference in tolerability
  - ~5% higher discontinuation rate in ibudilast group
- These results suggest activity of ibudilast in progressive MS and warrants further study in a phase 3 trial
- This study demonstrates the utility of advanced imaging methods in clinical trials to measure brain tissue integrity

SPRINT-MS

# Acknowledgements


Many thanks to:

- Clinical Coordinating Center – Massachusetts General Hospital
- Data Coordinating Center – University of Iowa
- Coordinating Support - Mellen Center for Multiple Sclerosis
- Protocol Steering Committee
- Site investigators
- NINDS and National MS Society for support throughout the study
- Participant protection:
  - Independent Medical Monitor Stephen Krieger, MD, Icahn School of Medicine, Mt Sinai
  - NINDS Data Safety Monitoring Board

Also, a very special thanks to all of the people living with progressive MS who participated in this trial


SPRINT-MS