HHS Public Access

Author manuscript

N Engl J Med. Author manuscript; available in PMC 2019 February 28.

Published in final edited form as:

N Engl J Med. 2018 August 30; 379(9): 846–855. doi:10.1056/NEJMoa1803583.

Phase 2 Trial of Ibudilast in Progressive Multiple Sclerosis

A full list of authors and affiliations appears at the end of the article.

Abstract

BACKGROUND—There are limited treatments for progressive multiple sclerosis. Ibudilast inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor, and toll-like receptor 4 and can cross the blood–brain barrier, with potential salutary effects in progressive multiple sclerosis.

METHODS—We enrolled patients with primary or secondary progressive multiple sclerosis in a phase 2 randomized trial of oral ibudilast (≤100 mg daily) or placebo for 96 weeks. The primary efficacy end point was the rate of brain atrophy, as measured by the brain parenchymal fraction (brain size relative to the volume of the outer surface contour of the brain). Major secondary end points included the change in the pyramidal tracts on diffusion tensor imaging, the magnetization transfer ratio in normal-appearing brain tissue, the thickness of the retinal nerve-fiber layer, and cortical atrophy, all measures of tissue damage in multiple sclerosis.

RESULTS—Of 255 patients who underwent randomization, 129 were assigned to ibudilast and 126 to placebo. A total of 53% of the patients in the ibudilast group and 52% of those in the placebo group had primary progressive disease; the others had secondary progressive disease. The rate of change in the brain parenchymal fraction was −0.0010 per year with ibudilast and −0.0019 per year with placebo (difference, 0.0009; 95% confidence interval, 0.00004 to 0.0017; P = 0.04), which represents approximately 2.5 ml less brain-tissue loss with ibudilast over a period of 96 weeks. Adverse events with ibudilast included gastrointestinal symptoms, headache, and depression.

CONCLUSIONS—In a phase 2 trial involving patients with progressive multiple sclerosis, ibudilast was associated with slower progression of brain atrophy than placebo but was associated with higher rates of gastrointestinal side effects, headache, and depression.

Even though more than a dozen therapies have been approved for the treatment of relapsing forms of multiple sclerosis, only the monoclonal antibody ocrelizumab and the chemotherapy agent mitoxantrone are approved for progressive multiple sclerosis.[1] Ibudilast is a small molecule available in Asia for the treatment of asthma and poststroke vertigo. Ibudilast inhibits several cyclic nucleotide phosphodiesterases, macrophage migration inhibitory factor,[2] and toll-like receptor 4 and can cross the blood–brain barrier, potentially having effects in the central nervous system.[3]

*A list of the NN102/SPRINT-MS Trial Investigators is provided in the Supplementary Appendix, available at NEJM.org.

Address reprint requests to Dr. Fox at the Mellen Center for Multiple Sclerosis, Cleveland Clinic, 9500 Euclid Ave., JJ36, Cleveland, OH 44195, or at foxr@ccf.org.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

Levels of macrophage migration inhibitory factor and toll-like receptor 4 are increased in the cerebrospinal fluid (CSF) of patients with progressive multiple sclerosis, and these proteins can elicit inflammatory responses in the central nervous system.[4–6] In a phase 2 trial involving patients with relapsing multiple sclerosis, ibudilast at a dose of 30 to 60 mg per day did not prevent the development of new lesions as shown on magnetic resonance imaging (MRI) but slowed the progression of brain atrophy in a dose-dependent fashion and decreased the proportion of gadolinium-enhancing lesions that converted to black holes on T_1-weighted images, the latter representing areas of severe brain-tissue injury.[7] These observations provided the equipoise for testing ibudilast as a possible therapy for progressive multiple sclerosis.[8]

One of the main purposes in the treatment of progressive multiple sclerosis is to slow the progression of neurologic impairment, which arises from permanent tissue injury.[9] A widely used measure of permanent tissue injury in multiple sclerosis is the degree of brain atrophy.[10] We report results of a phase 2, multicenter, randomized, double-blind, parallel-group trial (NeuroNEXT 102/Secondary and Primary Progressive Ibudilast NeuroNEXT Trial in Multiple Sclerosis [NN102/ SPRINT-MS]) that investigated the activity and safety of ibudilast as compared with placebo in progressive multiple sclerosis.[11]

METHODS

TRIAL OVERSIGHT

The trial was conducted by the Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), which is sponsored by the National Institute of Neurological Disorders and Stroke (NINDS). The trial was designed by a protocol working group and managed by a protocol steering committee, clinical coordinating center, and data coordinating center. Safety oversight was provided by an independent medical monitor, an NINDS-appointed data and safety monitoring board, and the NeuroNEXT central institutional review board, as summarized in the Supplementary Appendix (available with the full text of this article at NEJM.org). The data coordinating center at the University of Iowa maintained and analyzed the data. All the authors vouch for the adherence of the trial to the protocol (available at NEJM.org) and for the accuracy and completeness of the data and analysis and the reporting of adverse events.

The active drug and matching placebo were provided at no cost by MediciNova. MediciNova also provided less than 10% of the total trial funding, through an agreement with the National Institutes of Health, and had a representative on the protocol steering committee, who commented on protocol amendments and drafts of the manuscript. There was no confidentiality agreement between the authors and MediciNova; the protocol steering committee independently decided to submit the manuscript for publication.

The trial was conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice[12] and the Declaration of Helsinki.[13] All the patients provided written informed consent.

PATIENTS

Key eligibility criteria included an age of 21 to 65 years; diagnosis of primary progressive or secondary progressive multiple sclerosis according to 2010 International Panel criteria[14]; typical multiple sclerosis lesions on MRI according to Swanton's criteria, which require at least one demyelinating lesion in two or more of the following regions: periventricular, juxtacortical, infratentorial (brain stem and cerebellum), and spinal cord[15]; a score on the Expanded Disability Status Scale (EDSS)[16] of 3.0 to 6.5 (range, 0 to 10 in 0.5-point increments, with higher scores indicating more disability); and clinical evidence in the medical record of progression of disability in the preceding 2 years, as measured by an increase in the EDSS score of at least 0.5 points, an increase in the time to perform the timed 25-foot (7.6 m) walk of at least 20%, or an increase in the time to complete the 9-hole peg test of at least 20%.[17] Concurrent treatment with interferon beta-1 or glatiramer acetate was allowed.

Key exclusion criteria were clinical relapse or the use of systemic glucocorticoid treatment within 3 months before screening; concurrent use of immunomodulating therapies other than interferon beta-1 or glatiramer acetate; current use of medications that posed potential drug–drug interactions with ibudilast, including those that could prolong the QT interval; moderate-to-severe depression, as indicated by a score of 9 or higher on the Beck Depression Inventory–Fast Screen (range, 0 to 21, with higher scores indicating more severe depression)[18]; and an inability to lie sufficiently still in an MRI scanner to obtain high-quality images. For details on inclusion and exclusion criteria, see the Supplementary Appendix.

TRIAL DESIGN

Patients from 28 U.S. sites were randomly assigned (in a 1:1 ratio) to receive ibudilast at a dose of up to 100 mg orally (ten 10-mg capsules) per day or matching placebo pills in two or three divided doses for 96 weeks. The target dose was chosen on the basis, in part, of experience in trials of the drug for relapsing–remitting multiple sclerosis that used 60 mg per day[7] and evidence from preclinical studies that showed safety, acceptable adverse-event rates, high rates of adherence, and increased biologic activity in humans at 100 mg per day.[8]

After an initial 2-week period of 60 mg of ibudilast or matching placebo per day, the dose was increased to 100 mg of ibudilast or the equivalent number of placebo capsules per day. Dose adjustment for side effects including nausea, diarrhea, and vertigo to 60 mg, 80 mg, or 100 mg of ibudilast or equivalent placebo per day was allowed at the investigator's discretion up to week 8, after which patients maintained their then-current daily dose of the trial regimen. Safety visits were conducted every 4 weeks through week 12, then every 12 weeks through week 96. Adherence to the trial regimen was assessed by questioning patients and counting pills at clinical visits. Clinical disability according to the EDSS score was assessed every 24 weeks, at which time MRI and optical coherence tomography[19] were also performed.

Randomization was performed centrally with the use of an interactive Web-response system. Randomization was stratified according to disease type (primary or secondary progressive

multiple sclerosis) and concurrent use of immunomodulating therapy (yes [interferon beta-1 or glatiramer acetate] or no) with the use of a permuted block design with random block sizes of 4 or 6. All site investigators, image-analysis investigators, and patients were unaware of the trial-group assignments. At each trial site, examiners who were trained and certified by Neurostatus (Basel, Switzerland) in assessing the EDSS score conducted the neurologic examination; examiners were unaware of the trial-group assignments.

MRI was performed with Siemens (Trio/Prisma or Skyra) or GE (version 12x or higher) 3T systems. Image acquisition and quality assurance were overseen by a collaboration of three imageanalysis centers (see the Supplementary Appendix and protocol for details of image acquisition and quality assurance). Analysis of the thickness of the retinal nerve-fiber layer on optical coherence tomography was performed at a central reading center by two independent readers, and the measurements were averaged to give a final result (see the Supplementary Appendix for details).

TRIAL END POINTS

The primary end point was the rate of brain atrophy, as measured by the brain parenchymal fraction.[20] Safety was determined by site investigators reporting adverse events and serious adverse events; serious adverse events were reviewed by an independent medical monitor. The major secondary end points were disruption of tissue, as measured by change in pyramidal white-matter tracts on diffusion tensor imaging[21]; change in the magnetization transfer ratio in normal-appearing brain tissue[22]; change in the thickness of the retinal nerve-fiber layer on optical coherence tomography; and the rate of cortical atrophy, as measured by an algorithm for the detection of cortical longitudinal atrophy that has been described previously.[23]

The brain parenchymal fraction is the amount of brain tissue contained within a contour that surrounds the entire brain, including the CSF, as quantified from MRI data. The fraction is the proportion of cranial contents taken up by the brain and is normalized for different-sized heads. As atrophy progresses, CSF replaces brain tissue and the brain parenchymal fraction decreases. Diffusion tensor imaging measures the threedimensional diffusion of water, with increased diffusivity in areas of tissue injury[21]; the magnetization transfer ratio measures the transfer of magnetization between hydrogen atoms in tissue and hydrogen atoms in the surrounding water and is decreased in areas of tissue injury or loss[24]; and thinning of the cortical gray matter can be measured from MRI data.[23] The optic nerve is also commonly injured in patients with multiple sclerosis, and this injury can be quantitated by determining the thickness of the retinal nervefiber layer on optical coherence tomography.[25]

Additional secondary end points included the progression of disability as measured by the EDSS score.[16] Confirmed disability progression was defined as an increase in the EDSS score of at least 1.0 point from baseline (or an increase of ≥0.5 points for patients with a baseline EDSS score of >5.0) that was sustained for at least 20 weeks.

STATISTICAL ANALYSIS

Efficacy analyses were performed on data from the modified intention-to-treat population, which was defined as all the patients who underwent randomization, received at least one

dose of a trial regimen, and had at least one efficacy assessment after baseline. Safety analyses were performed on data from all the patients who received at least one dose of a trial regimen. Imaging end points were assessed for differences in rates of change between the trial groups over time with the use of linear mixed models, under an assumption that missing data were missing at random.[26] Nonlinear models of change in brain volume over time did not perform as well as the linear model. Sensitivity analyses included the effects of covariates that were imbalanced at baseline and a per-protocol analysis, which included patients with no major protocol deviations and 75 to 125% adherence to the trial regimen and which used only data collected before any early discontinuation of the trial regimen.

Because the statistical analysis plan did not include a provision for correcting for multiple comparisons when tests were conducted for secondary or other end points, those results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects for secondary end points. Safety and side-effect profile were assessed with the use of logistic and Poisson regression models that were adjusted for disease type and concurrent use or nonuse of immunomodulating therapy. The end point of 20week confirmed disability progression according to the EDSS score was evaluated with the use of Cox proportional-hazards regression, with adjustment for disease type and concurrent use or nonuse of immunomodulating therapy. Betweengroup differences in baseline characteristics were analyzed with the use of Student’s t-test or a Wilcoxon rank-sum test for continuous variables and a chi-square test or Fisher’s exact test for nominal variables. For details regarding the statistical analysis, see the Supplementary Appendix and statistical analysis plan (available with the protocol).

RESULTS

PATIENTS

Of 255 patients who underwent randomization, 129 were assigned to receive ibudilast and 126 to receive placebo (Fig. S1 in the Supplementary Appendix). Baseline demographic and clinical characteristics were similar in the two trial groups except that the ibudilast group was younger and had lower transverse diffusivity (one measure of tissue disruption on diffusion tensor imaging) than the placebo group (Table 1). A total of 53% of the patients in the ibudilast group and 52% of those in the placebo group had primary progressive multiple sclerosis.

A total of 8 patients (6%) receiving ibudilast and 3 (2%) receiving placebo withdrew from the trial without at least one postbaseline MRI scan for efficacy assessment and were not included in the protocol-defined modified intention-to-treat population. Thus, 244 patients (121 in the ibudilast group and 123 in the placebo group) were included in the primary and major secondary imaging analyses. After 2 months of the intervention period, full target dosing (10 capsules per day) was achieved in 112 of 121 patients (93%) in the ibudilast group and 120 of 122 patients (98%) in the placebo group. A total of 108 of 129 patients (84%) in the ibudilast group and 112 of 126 patients (89%) in the placebo group completed the 96-week trial.

END-POINT RESULTS

The estimated rate of change in the brain parenchymal fraction was −0.0010 per year with ibudilast (95% confidence interval [CI], −0.0016 to −0.0004) and −0.0019 per year with placebo (95% CI, −0.0025 to −0.0013) (Fig. 1). This represented an absolute difference of 0.0009 per year (95% CI, 0.00004 to 0.0017; P = 0.04), or approximately 2.5 ml less brain-tissue loss with ibudilast than with placebo over a period of 96 weeks, and a relative difference of 48%. The per-protocol analysis of the primary end point was consistent with the primary analysis (P = 0.03), as was a sensitivity analysis with adjustment for age at baseline (P = 0.03). The results of all other prespecified sensitivity analyses were in the same direction for the difference between the two groups.

The results of major secondary imaging end points are shown in Table 2. In analyses that were not adjusted for multiple comparisons, the 95% confidence intervals for the differences between trial groups overlapped zero, except for cortical thickness and magnetization transfer ratio. The hazard ratio for 20-week confirmed disability progression (as measured by the EDSS score) with ibudilast as compared with placebo was 0.74, with a 95% confidence interval overlapping 1.00 (Fig. 2).

SAFETY

The percentage of patients reporting an adverse event was 92% with ibudilast and 88% with placebo (P = 0.26) (Table 3). Adverse events with a higher incidence in the ibudilast group than in the placebo group (P≤0.10) were gastrointestinal symptoms (nausea, diarrhea, abdominal pain, and vomiting) and depression. The frequency of headaches (total number of headaches per unit of time) was higher in the ibudilast group than in the placebo group (P = 0.09). There was no meaningful difference in the rates or types of infections between the trial groups. The percentage of patients reporting a serious adverse event was 16% with ibudilast and 19% with placebo (P = 0.46) (Table 3, and Table S1 in the Supplementary Appendix). There were no deaths and no opportunistic infections during the trial period.

The percentage of patients who withdrew from the trial was 16% with ibudilast and 11% with placebo (P = 0.24); a total of 8% and 4%, respectively, withdrew owing to adverse events (P = 0.21). A total of 71 patients discontinued the trial regimen because of either withdrawal from the trial or early cessation of the trial regimen (30% in the ibudilast group and 25% in the placebo group, P = 0.39). Of these, 29 patients withdrew from the trial but continued to receive the trial regimen up to the time of withdrawal, 6 withdrew from the trial after previously stopping the trial regimen, and 36 stopped the trial regimen early but continued follow-up within the trial. Of these 71 patients, 38 indicated that discontinuation of the trial regimen or withdrawal from the trial was due to one or more adverse events (18% in the ibudilast group and 12% in the placebo group, P = 0.18).

DISCUSSION

In this phase 2 trial involving patients with primary or secondary progressive multiple sclerosis, the progression of brain atrophy over a period of 96 weeks was slower with the small molecule ibudilast than with placebo. Although clinical trials in multiple sclerosis use

a variety of methods to measure brain atrophy, the 48% difference in atrophy progression favoring ibudilast in the current trial can be broadly compared with results from other trials in progressive multiple sclerosis — for example, 17.5% slowing of brain atrophy with ocrelizumab,[27] 15% slowing with siponimod,[28] and 43% slowing with simvastatin.[29] Because the current trial did not make comparisons with these drugs, no conclusions can be made about relative effects on brain atrophy.

The rate of brain atrophy in the placebo group of our trial was less than the rate reported in a longitudinal study involving patients with secondary progressive multiple sclerosis[30] that used the same method to measure brain atrophy. This difference may be explained by our patients being older and having a longer duration of disease than patients with progressive multiple sclerosis who were involved in previous trials[27–29] and by the fact that nearly one third of our patients took either glatiramer acetate or interferon beta-1, agents that slow progression of brain atrophy, or it may represent the play of chance in different patient populations among studies.

The clinical effect of slowing the progression of brain atrophy in progressive multiple sclerosis is not well understood, which makes the clinical relevance of our findings unknown. The decline in disability progression was similar in the two trial groups over a period of 96 weeks in the current trial.

For the additional secondary imaging end points, the 95% confidence intervals of the difference in slopes of change between trial groups did not include zero for the magnetization transfer ratio and cortical atrophy, although the analyses were not adjusted for multiple comparisons, which limits their interpretation. Although measures of cortical atrophy are similar conceptually to measures of whole-brain atrophy, post hoc analysis in our trial showed a correlation of 0.41 between them, which suggests that these two measures have a limited quantitative association.

Gastrointestinal symptoms were the most common adverse events with ibudilast. Depression was more common with ibudilast than with placebo, but there were no reports of suicidality or suicide. Rates of discontinuation of the trial regimen or of the trial were 5 to 6 percentage points higher with ibudilast than with placebo.

The best outcome metrics for phase 2 trials in progressive multiple sclerosis have not been established. Whole-brain atrophy is commonly used in clinical trials[10] but is limited by its slow change over time, physiologic variability (i.e., changes with hydration[31]), and the fact that it provides only one value per patient per time point. This trial provides data from five advanced imaging metrics that may contribute to the methods in future trials of progressive multiple sclerosis.

In conclusion, this phase 2 trial in progressive multiple sclerosis showed slower rates of overall brain atrophy with ibudilast than with placebo. The drug was associated with gastrointestinal and other side effects. Further trials are needed to identify whether the effect on brain atrophy is reproducible and is associated with slowed progression of neurologic disability.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Authors

Robert J. Fox, M.D., Christopher S. Coffey, Ph.D., Robin Conwit, M.D., Merit E. Cudkowicz, M.D., Trevis Gleason, B.S., Andrew Goodman, M.D., Eric C. Klawiter, M.D., Kazuko Matsuda, M.D., Michelle McGovern, B.S., Robert T. Naismith, M.D., Akshata Ashokkumar, M.S., Janel Barnes, Ph.D., Dixie Ecklund, M.S.N., Elizabeth Klingner, M.S., Maxine Koepp, J.D., Jeffrey D. Long, Ph.D., Sneha Natarajan, Ph.D., Brenda Thornell, B.S., Jon Yankey, M.S, Robert A. Bermel, M.D., Josef P. Debbins, Ph.D., Xuemei Huang, M.S., Patricia Jagodnik, M.B.A., Mark J. Lowe, Ph.D., Kunio Nakamura, Ph.D., Sridar Narayanan, Ph.D., Ken E. Sakaie, Ph.D., Bhaskar Thoomukuntla, M.S., M.B.A., Xiaopeng Zhou, Ph.D., Stephen Krieger, M.D., Enrique Alvarez, M.D., Ph.D., Michelle Apperson, M.D. Ph.D., Khurram Bashir, M.D., Bruce A. Cohen, M.D., Patricia K. Coyle, M.D., Silvia Delgado, M.D., L. Dana Dewitt, M.D., Angela Flores, M.D., Barbara S. Giesser, M.D., Myla D. Goldman, M.D., Burk Jubelt, M.D., Neil Lava, M.D., Sharon G. Lynch, M.D., Harold Moses, M.D., Daniel Ontaneda, M.D., Jai S. Perumal, M.D., Michael Racke, M.D., Pavle Repovic, M.D., Ph.D., Claire S. Riley, M.D., Christopher Severson, M.D., Shlomo Shinnar, M.D., Ph.D., Valerie Suski, D.O., Bianca Weinstock-Guttman, M.D., Vijayshree Yadav, M.D., and Aram Zabeti, M.D.

for the NN102/SPRINT-MS Trial Investigators[*]

Affiliations

Mellen Center for Multiple Sclerosis, Neurological Institute (R.J.F., S. Natarajan, R.A.B., D.O.), the Imaging Institute (X.H., M.J.L., K.E.S., X.Z.), and the Department of Biomedical Engineering (P.J., K.N., B. Thoomukuntla), Cleveland Clinic, Cleveland, Ohio State University, Columbus (M.R.), and University of Cincinnati, Cincinnati (A.Z.) — all in Ohio; the Data Coordinating Center, Network for Excellence in Neuroscience Clinical Trials (NeuroNEXT), University of Iowa, Iowa City (C.S.C., J.B., D.E., E.K., M.K., J.D.L., J.Y.); the National Institute of Neurological Disorders and Stroke, Bethesda, MD (R.C.); the Clinical Coordinating Center, NeuroNEXT, Massachusetts General Hospital, Neurological Clinical Research Institute, Harvard Partners (M.E.C., M.M., A.A., B. Thornell), the Department of Neurology, Massachusetts General Hospital, Harvard Medical School (E.C.K.), and Brigham and Women's Hospital (C.S.), Boston; patient advocate (T.G.) and Swedish Medical Center at Seattle (P.R.), Seattle; University of Rochester Medical Center, Rochester (A.G.), Corinne Goldsmith Dickinson Center for Multiple Sclerosis, Mount Sinai Medical Center (S.K.), Weill Cornell Medical College (J.S.P.), Columbia University Medical Center (C.S.R.), and Montefiore Medical Center, Albert Einstein College of Medicine (S.S.), New York, State University of New York (SUNY) at Stony Brook, Stony Brook (P.K.C.), SUNY Upstate Medical University, Syracuse (B.J.), and SUNY at Buffalo, Buffalo (B.W.-G.) — all in New York; MediciNova, La Jolla (K.M.), University of California at Davis, Sacramento (M.A.), and University of California at

Los Angeles, Los Angeles (B.S.G.) — all in California; Washington University School of Medicine, St. Louis (R.T.N.); Barrow Neurological Institute, St. Joseph's Hospital and Medical Center, Phoenix, AZ (J.P.D.); NeuroRx Research, Montreal (S. Narayanan); the School of Health Sciences, College of Health and Human Sciences, Purdue University, West Lafayette, IN (X.Z.); University of Colorado Denver, Aurora (E.A.); University of Alabama at Birmingham, Birmingham (K.B.); Feinberg School of Medicine, Northwestern University, Chicago (B.A.C.); University of Miami Miller School of Medicine, Miami (S.D.); University of Utah, Salt Lake City (L.D.D.); University of Texas Southwestern Medical Center, Dallas (A.F.); University of Virginia at Charlottesville, Charlottesville (M.D.G.); Emory University, Atlanta (N.L.); University of Kansas Medical Center, Kansas City (S.G.L.); Vanderbilt University, Nashville (H.M.); University of Pittsburgh Medical Center, Pittsburgh (V.S.); and Oregon Health and Science University, Portland (V.Y.).

Acknowledgments

The content of this article is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supported by grants from the National Institute of Neurological Disorders and Stroke (NINDS) (U01NS082329) and the National Multiple Sclerosis Society (RG 4778-A-6) and by MediciNova through a contract with the National Institutes of Health (NIH). The NeuroNEXT Network is supported by the NINDS (Central Coordinating Center, U01NS077179; Data Coordinating Center, U01NS077352; and individual grants to each trial site). Research reported in this article was also supported by grants from the National Center for Advancing Translational Sciences of the NIH to Case Western Reserve University (UL1 TR000439), Columbia University Medical Center (UL1 TR 000040), Montefiore Medical Center (UL1 TR002556), Oregon Health and Science University (UL1TR0002369), University of Cincinnati (UL1 TR001425–03), University of Colorado Denver (KL2 TR001080), Washington University in St. Louis (UL1 TR000448), and Weill Cornell Medical Center (UL1 TR000457).

We thank the persons with multiple sclerosis who made this trial possible by volunteering to participate, as well as their families and friends who supported their involvement in the trial.

(Funded by the National Institute of Neurological Disorders and Stroke and others; NN102/SPRINT-MS ClinicalTrials.gov number, NCT01982942.)

REFERENCES

1. Ocrevus: EPAR product information. London: European Medicines Agency, 2018 (http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/004043/WC500241126.pdf).
2. Cho Y, Crichlow GV, Vermeire JJ, et al. Allosteric inhibition of macrophage migration inhibitory factor revealed by ibudilast. Proc Natl Acad Sci U S A 2010; 107: 11313–8. [PubMed: 20534506]
3. Ruiz-Pérez D, Benito J, Polo G, et al. The effects of the toll-like receptor 4 antagonist, ibudilast, on sevoflurane's minimum alveolar concentration and the delayed remifentanil-induced increase in the minimum alveolar concentration in rats. Anesth Analg 2016; 122: 1370–6. [PubMed: 26859874]
4. Hagman S, Raunio M, Rossi M, Dastidar P, Elovaara I. Disease-associated inflammatory biomarker profiles in blood in different subtypes of multiple sclerosis: prospective clinical and MRI follow-up study. J Neuroimmunol 2011; 234: 141–7. [PubMed: 21397339]
5. Su Y, Wang Y, Zhou Y, et al. Macrophage migration inhibitory factor activates inflammatory responses of astrocytes through interaction with CD74 receptor. Oncotarget 2017; 8:2719–30. [PubMed: 27926507]
6. Andersson A, Covacu R, Sunnemark D, et al. Pivotal advance: HMGB1 expression in active lesions of human and experimental multiple sclerosis. J Leukoc Biol 2008; 84:1248–55. [PubMed: 18644848]

7. Barkhof F, Hulst HE, Drulovic J, Uitdehaag BM, Matsuda K, Landin R. Ibudilast in relapsing-remitting multiple sclerosis: a neuroprotectant? Neurology 2010;74: 1033–40. [PubMed: 20200338]
8. Johnson KW, Matsuda K, Iwaki Y. Ibudilast for the treatment of drug addiction and other neurological conditions. Clin Invest 2014; 4: 269–79.
9. Khaleeli Z, Ciccarelli O, Manfredonia F, et al. Predicting progression in primary progressive multiple sclerosis: a 10-year multicenter study. Ann Neurol 2008;63: 790–3. [PubMed: 18383506]
10. Moccia M, de Stefano N, Barkhof F. Imaging outcome measures for progressive multiple sclerosis trials. Mult Scler 2017; 23: 1614–26. [PubMed: 29041865]
11. Fox RJ, Coffey CS, Cudkowicz ME, et al. Design, rationale, and baseline characteristics of the randomized double-blind phase II clinical trial of ibudilast in progressive multiple sclerosis. Contemp Clin Trials 2016; 50: 166–77. [PubMed: 27521810]
12. International Council for Harmonisa-tion of Technical Requirements for Pharmaceuticals for Human Use. Integrated addendum to ICH E6(R1): guideline for good clinical practice E6(R2). November 2016 (http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf).
13. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 2013;310: 2191–4. [PubMed: 24141714]
14. Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69: 292–302. [PubMed: 21387374]
15. Swanton JK, Rovira A, Tintore M, et al. MRI criteria for multiple sclerosis in patients presenting with clinically isolated syndromes: a multicentre retrospective study. Lancet Neurol 2007; 6:677–86. [PubMed: 17616439]
16. Kurtzke JF. On the origin of EDSS. Mult Scler Relat Disord 2015; 4: 95–103. [PubMed: 25787185]
17. Ontaneda D, LaRocca N, Coetzee T, Rudick R. Revisiting the multiple sclerosis functional composite: proceedings from the National Multiple Sclerosis Society (NMSS) Task Force on Clinical Disability Measures. Mult Scler 2012; 18: 1074–80. [PubMed: 22740488]
18. Neitzer A, Sun S, Doss S, Moran J, Schiller B. Beck Depression InventoryFast Screen (BDI-FS): an efficient tool for depression screening in patients with endstage renal disease. Hemodial Int 2012; 16:207–13. [PubMed: 22754932]
19. Petzold A, de Boer JF, Schippling S, et al. Optical coherence tomography in multiple sclerosis: a systematic review and meta-analysis. Lancet Neurol 2010;9 :921–32. [PubMed: 20723847]
20. Fisher E, Cothren RM, Tkach JA, Masaryk TJ, Cornhill JF. Knowledge-based 3D segmentation of MR images for quantitative MS lesion tracking. SPIE Medical Imaging 1997; 3034:599–610.
21. Fox RJ, Cronin T, Lin J, et al. Measuring myelin repair and axonal loss with diffusion tensor imaging. AJNR Am J Neuroradiol 2011; 32:85–91. [PubMed: 20947644]
22. Brown RA, Narayanan S, Arnold DL. Segmentation of magnetization transfer ratio lesions for longitudinal analysis of demyelination and remyelination in multiple sclerosis. Neuroimage 2013; 66: 103–9. [PubMed: 23110887]
23. Nakamura K, Fox R, Fisher E. CLADA: cortical longitudinal atrophy detection algorithm. Neuroimage 2011; 54: 278–89. [PubMed: 20674750]
24. Richert ND, Ostuni JL, Bash CN, Leist TP, McFarland HF, Frank JA. Interferon beta-1b and intravenous methylprednisolone promote lesion recovery in multiple sclerosis. Mult Scler 2001; 7: 49–58. [PubMed: 11321194]
25. Talman LS, Bisker ER, Sackel DJ, et al. Longitudinal study of vision and retinal nerve fiber layer thickness in multiple sclerosis. Ann Neurol 2010; 67: 749–60. [PubMed: 20517936]
26. Verbeke G, Molenberghs G. Linear mixed models for longitudinal data. New York: Springer, 2000.
27. Montalban X, Hauser SL, Kappos L,et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. N Engl J Med 2017; 376:209–20. [PubMed: 28002688]
28. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. Lancet 2018; 391:1263–73. [PubMed: 29576505]

29. Chataway J, Schuerer N, Alsanousi A, et al. Effect of high-dose simvastatin on brain atrophy and disability in secondary progressive multiple sclerosis (MS-STAT): a randomised, placebo-controlled, phase 2 trial. Lancet 2014; 383: 2213–21. [PubMed: 24655729]

30. Fisher E, Lee JC, Nakamura K, Rudick RA. Gray matter atrophy in multiple sclerosis: a longitudinal study. Ann Neurol 2008;64:255–65. [PubMed: 18661561]

31. Duning T, Kloska S, Steinsträter O, Kugel H, Heindel W, Knecht S. Dehydration confounds the assessment of brain atrophy. Neurology 2005;64: 548–50. [PubMed: 15699394]

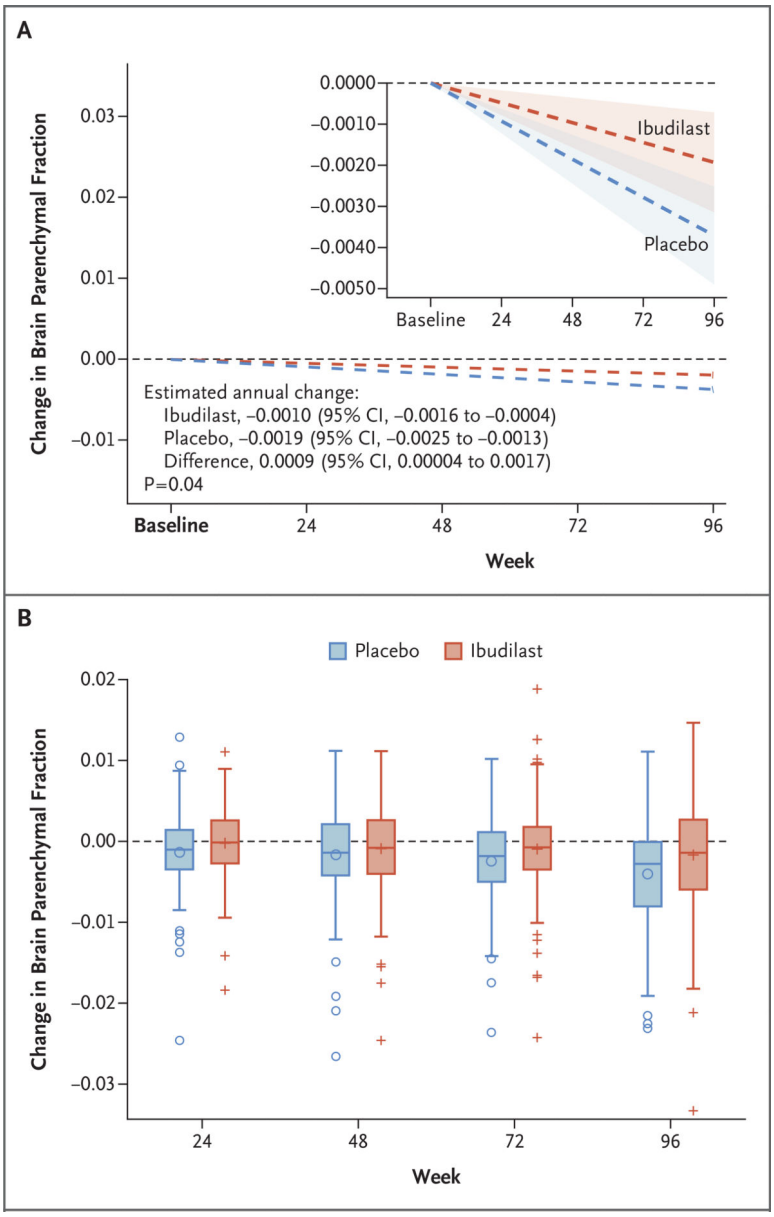

Figure 1. Change in Whole-Brain Atrophy.

Panel A shows the change in whole-brain atrophy in each trial group as derived from a linear mixed model. Change was measured according to the mean brain parenchymal fraction between baseline and week 96 with the use of all available data. The inset shows the same data on an enlarged y axis, with shaded areas indicating 95% confidence intervals of the estimated slope. Panel B shows box-and-whisker plots of change in whole-brain atrophy at each time point. The upper and lower edges of the boxes correspond to the 75th and 25th percentiles, respectively. Within the boxes, the circles (for placebo) and plus signs (for ibudilast) correspond to the mean and the horizontal lines correspond to the 50th percentile (median). The upper and lower ends of the whiskers correspond to the highest value within 1.5 times the interquartile range of the 75th percentile and the lowest value within 1.5 times the interquartile range of the 25th percentile, respectively. The circles and plus signs outside

the whiskers indicate outliers. In both panels, the black dashed horizontal line represents a value of no change in the brain parenchymal fraction.

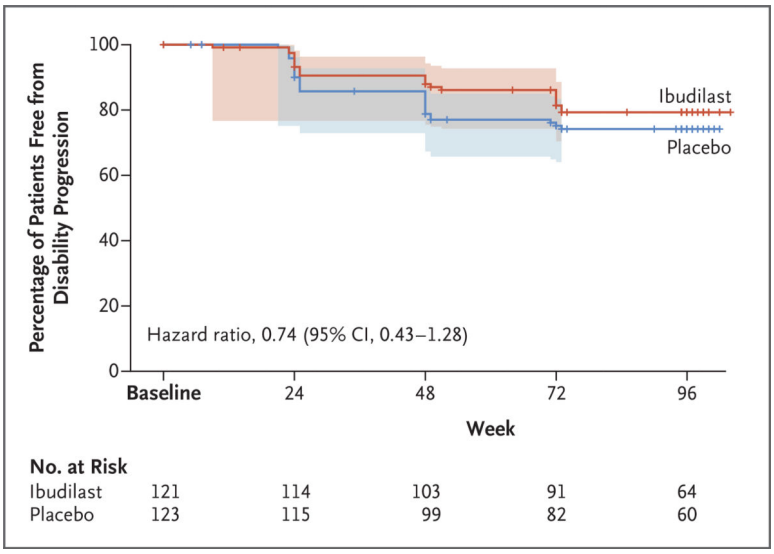

Figure 2. Disability Progression That Was Sustained for at Least 20 Weeks.

In this analysis, progression of disability was measured according to the score on the Expanded Disability Status Scale (EDSS; range, 0 to 10 in 0.5-point increments, with higher scores indicating more disability) with the use of Cox proportional-hazards regression. Confirmed disability progression was defined as an increase in the EDSS score of at least 1.0 point from baseline (or an increase of ≥0.5 points for patients with a baseline EDSS score of >5.0) that was sustained for at least 20 weeks. Shaded areas indicate 95% confidence intervals. Tick marks indicate censored data. The estimated number of patients at risk for disability progression in each group at each time point is given below the graph.

Table 1.

Baseline Demographic and Clinical Characteristics.*

Characteristic	Placebo (N = 126)	Ibudilast (N = 129)
Age — yr	57±7	55±8
Female sex — no. (%)	69 (55)	67 (52)
Race — no. (%)†		
White	114 (90)	122 (95)
Black	7 (6)	4 (3)
Other	1 (1)	3 (2)
Unknown or not reported	4 (3)	0
Hispanic ethnic group — no. (%)†	3 (2)	4 (3)
Primary progressive disease — no. (%)	66 (52)	68 (53)
Use of injectable immunomodulating therapy — no. (%)	40 (32)	40 (31)
Glatiramer acetate	24 (19)	19 (15)
Interferon beta-1	16 (13)	21 (16)
Duration of disease — yr		
Median	9	11
Range	0–36	0–41
EDSS score‡		
Median	6.0	6.0
Range	3.0–7.0	2.5–6.5
Timed 25-ft walk — sec		
Median	9.93	9.35
Range	3.60–180.00	4.05–73.50
9-Hole peg test — sec		
Median	30.31	28.68
Range	16.58–201.88	17.58–171.73
Symbol Digit Modalities Test — no. of correct answers§	41.67±14.04	43.41±14.62
Low-contrast visual acuity test — no. of correct answers¶	26.85±12.78	29.09±12.53
Brain parenchymal fraction	0.80±0.03	0.80±0.03
Volume of lesions on T_2-weighted images — cm^3	10±11	10±11
Magnetization transfer ratio in normal-appearing brain tissue — normalized units‖	0.31±0.31	0.29±0.25
Cortical thickness — mm	3.03±0.22	3.04±0.23
Longitudinal diffusivity on diffusion tensor imaging — 10^{-3} mm^2/sec	1.24±0.05	1.25±0.06
Transverse diffusivity on diffusion tensor imaging — 10^{-3} mm^2/sec	0.56±0.04	0.55±0.04
Thickness of the retinal nerve-fiber layer — μm**	81.15±13.15	83.15±10.81

*Plus–minus values are means ±SD. There were no significant differences (P>0.05) between the two groups except for age (P = 0.02) and transverse diffusivity on diffusion tensor imaging (P = 0.04). The P value for continuous variables was calculated with Student's t-test, except the comparisons for duration of disease, score on the Expanded Disability Status Scale (EDSS), timed 25-foot (7.6 m) walk, and 9-hole peg test, which were made with a Wilcoxon rank-sum test. The P value for nominal variables was calculated with a chi-square test, except the comparisons for race and Hispanic ethnic group, which were made with Fisher's exact test.

[†] Race and ethnic group were reported by the patients.

[‡] Scores on the EDSS range from 0 to 10 in 0.5-point increments, with higher scores indicating more disability.

[§] Scores on the Symbol Digit Modalities Test range from 0 to 110, with higher scores indicating higher cognitive performance.

[¶] Scores on the low-contrast visual acuity test range from 0 to 60, with higher scores indicating greater ability to read small letters on a 2.5% low-contrast eye chart.

[‖] Data on the magnetization transfer ratio were not available for one patient in the placebo group and two patients in the ibudilast group.

[**] Values for the thickness of the retinal nerve-fiber layer were the mean of the left and right eye measures. When measures from both eyes were unavailable, the value for the one available eye was used. Data on the thickness of the retinal nervefiber layer of both eyes were missing for four patients in the placebo group and five patients in the ibudilast group.

Table 2.

Primary and Major Secondary End Points over a Period of 96 Weeks.*

End Point	Placebo	Ibudilast	Difference (95% CI)
	estimated annual rate of change over 96-wk period (95% CI)		
Primary end point: brain parenchymal fraction	−0.0019 (−0.0025 to −0.0013)	−0.0010 (−0.0016 to −0.0004)	0.0009 (0.00004 to 0.0017)†
Major secondary end points			
Transverse diffusivity in corticospinal tracts — 10^{-3} mm^2/sec	0.0015 (−0.0013 to 0.0043)	−0.0015 (−0.0043 to 0.0014)	−0.0029 (−0.0069 to 0.0010)
Longitudinal diffusivity in corticospinal tracts — 10^{-3} mm^2/sec	−0.0007 (−0.0039 to 0.0025)	0.0001 (−0.0032 to 0.0033)	0.0008 (−0.0037 to 0.0053)
Magnetization transfer ratio in normal-appearing brain tissue	−0.0282 (−0.0469 to −0.0095)	−0.0051 (−0.0242 to 0.0139)	0.0231 (0.0003 to 0.0458)
Retinal nerve fiber layer — μm	−0.2630 (−0.5973 to 0.0714)	0.0424 (−0.3091 to 0.3939)	0.3054 (−0.1786 to 0.7893)
Cortical thickness — mm	−0.0105 (−0.0146 to −0.0065)	−0.0019 (−0.0061 to 0.0022)	0.0086 (0.0028 to 0.0144)

*Because the statistical analysis plan did not include a provision for correcting for multiple comparisons when tests were conducted for secondary or other end points, results are reported as point estimates and 95% confidence intervals. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used to infer definitive treatment effects for secondary end points.

†P = 0.04.

Table 3.

Adverse Events, Trial Discontinuation, and Serious Adverse Events.*

Event	Placebo (N = 126)	Ibudilast (N = 129)	P Value
	no. of patients (%)		
Any adverse event	111 (88)	119 (92)	0.26
Gastrointestinal event			
Abdominal pain	0	6 (5)†	0.03
Abdominal pain, upper	0	5 (4)†	0.06
Diarrhea	9 (7)	21 (16)†	0.03
Nausea	19 (15)	35 (27)†	0.02
Vomiting	3 (2)	9 (7)†	0.10
Fatigue	11 (9)	14 (11)	0.57
Infection			
Skin infection	7 (6)†	1 (1)	0.06
Upper respiratory tract infection	24 (19)†	13 (10)	0.05
Urinary tract infection	41 (33)	35 (27)	0.34
Fall	20 (16)	29 (22)	0.18
Musculoskeletal event			
Back pain	15 (12)	10 (8)	0.27
Neck pain	4 (3)†	0	0.06
Pain in the arms or legs	13 (10)†	5 (4)	0.05
Headache	15 (12)	23 (18)‡	0.19
Psychiatric event			
Depression	4 (3)	12 (9)†	0.05
Insomnia	11 (9)	14 (11)	0.57
Withdrawal from the trial			
For any reason	14 (11)	21 (16)	0.24
Owing to adverse event	5 (4)	10 (8)	0.21
Serious adverse event	24 (19)	20 (16)	0.46

*Shown are adverse events with an incidence of more than 10% in either group or a difference in incidence between groups (P≤0.10).

†The incidence was higher than that in the other group (P≤0.10).

‡The frequency of headaches (total number of headaches per unit of time) was higher in the ibudilast group than in the placebo group (P = 0.09).