A Phase 3 Trial of Extended Release Oral Dalfampridine in Multiple Sclerosis

Andrew D. Goodman, MD,1 Theodore R. Brown, MD, MPH,2 Keith R. Edwards, MD,3 Lauren B. Krupp, MD,4 Randall T Schapiro, MD,5 Ron Cohen, MD,6 Lawrence N. Marinucci, MS,6 and Andrew R. Blight, PhD6 on behalf of the MSF204 Investigators

Objective: A previous phase 3 study showed significant improvement in walking ability in multiple sclerosis (MS) patients treated with oral, extended-release dalfampridine (4-aminopyridine) 10mg twice daily. The current study was designed to confirm efficacy and further define safety and pharmacodynamics.

Methods: This was a 39-center, double-blind trial in patients with definite MS of any course type. Participants were randomized to 9 weeks of treatment with dalfampridine (10mg twice daily; n = 120) or placebo (n = 119). Response was defined as consistent improvement on the Timed 25-Foot Walk, with percentage of timed walk responders (TWRs) in each treatment group as the primary outcome. The last on-treatment visit provided data from 8 to 12 hours postdose, to examine maintenance of effect.

Results: One patient from each group was excluded from the modified Intention to Treat population. The proportion of TWRs was higher in the dalfampridine group (51/119 or 42.9%) compared to the placebo group (11/118 or 9.3%, p < 0.0001). The average improvement in walking speed among dalfampridine-treated TWRs during the 8-week efficacy evaluation period was 24.7% from baseline (95% confidence interval, 21.0–28.4%); the mean improvement at the last on-treatment visit was 25.7%, showing maintenance of effect over the interdosing period. There were no new safety findings.

Interpretation: This interventional study provides class 1 evidence that dalfampridine extended-release tablets produce clinically meaningful improvement in walking ability in a subset of people with MS, with the effect maintained between doses.

Dalfampridine (4-aminopyridine) represents a potentially novel class of therapy for multiple sclerosis (MS) that directly targets the nervous system, modifying the function of axons demyelinated by the disease. A previous phase 3 trial indicated that treatment with extended-release tablets of dalfampridine, 10mg twice a day, improves walking ability in some people with MS, and that this provides a meaningful therapeutic benefit.1 The current study was designed to confirm those results and to determine whether the improvement in walking is maintained between doses. Earlier studies evaluated treatment with dalfampridine in various neurological functions affected by MS,2–7 but most of these did not allow for unbiased assessment of safety and efficacy, as reflected in an independent review in 2002.8 More recently, a series of 4 clinical trials, including 2 phase 3 studies, of which this is the second, have focused on walking ability, measured with the Timed 25-Foot Walk (T25FW).1,9,10

---

View this article online at wileyonlinelibrary.com. DOI: 10.1002/ana.22240

Presented in part at the World Congress on Treatment and Research in Multiple Sclerosis, Montreal, Quebec, Canada, September 20, 2008.

The following individuals served as members of the independent Data Monitoring Committee: Dr J. Selzer (chair), Dr B. Greenberg, Dr A. Hartman, and A. Smith (statistician).

Received Jan 27, 2010, and in revised form Aug 19, 2010. Accepted for publication Aug 27, 2010.

Address correspondence to Dr Goodman, Department of Neurology, University of Rochester Medical Center, 601 Elmwood Avenue, Room 6-8521, Box 605, Rochester, NY 14642. E-mail: andrew_goodman@urmc.rochester.edu

From the 1University of Rochester, Rochester, NY; 2Evergreen Hospital Medical Center, Kirkland, WA; 3Neurological Research Center, Bennington, VT; 4Stony Brook University, Stony Brook, NY; 5Minneapolis Clinic of Neurology, Minneapolis, MN; 6Acorda Therapeutics, Inc., Hawthorne, NY.
These studies used an extended-release, oral tablet formulation, previously referred to as Fampridine-SR, designed to maintain therapeutic plasma concentrations with twice daily dosing.\textsuperscript{11,12}

The US Food and Drug Administration (FDA) recently determined that the previously accepted US Adopted Name (USAN, or nonproprietary name) fampridine was too similar to the name of another approved medication and could lead to medical errors. The FDA therefore requested the name to be changed, and the USAN Council has changed the nonproprietary name to dalfampridine. In addition, the FDA has determined that the term extended release will be used to refer to this formulation rather than the term sustained release, which has been applied in earlier publications. These new naming conventions are used here.

**Patients and Methods**

**Patient Selection**

Patients were selected from 39 centers in the United States and Canada. Eligible patients were aged 18 to 70 years, had clinically defined MS,\textsuperscript{13} and had a T25FW time between 8 and 45 seconds. Patients were excluded if they had prior exposure to dalfampridine, MS exacerbation within 60 days, a history of seizures, evidence of epileptiform activity on an electroencephalogram, or any condition that would interfere with study conduct. Additional restrictions on changes in concomitant medications were designed to avoid possible related changes in MS symptoms. The trial was performed in accordance with the Declaration of Helsinki and its subsequent amendments, Good Clinical Practice, and applicable regulatory requirements. The protocol was approved by the institutional review boards or ethics committees, and all participants gave written informed consent. The Trial Registration Identifier is NCT00483652 (clinicaltrials.gov).

**Protocol and Patient Assessment**

This was a randomized, double-blind, placebo-controlled trial. Patients underwent screening, and eligible patients returned 1 week later (Visit 0; Fig 1), then entered a 2-week, single-blind, placebo run-in period. Patients were instructed to take 1 blinded tablet (supplied in appropriate quantities at each clinic visit) approximately every 12 hours during the treatment phase.

At Visit 2, patients were randomized equally to either extended release dalfampridine (10mg twice daily) or placebo, using a predetermined, computer-generated randomization schedule, blocked and stratified by treatment site. Following randomization, patients returned every 2 weeks for evaluation at Visits 3 to 6, and were then instructed to return in 1 week for Visit 7 and to time their last dose of study medication such that this visit would allow assessments to be made between 10 and 12 hours after this dose. Follow-up assessments were obtained 2 weeks later, at Visit 8.

The primary measure of efficacy was based on walking speed, measured by the T25FW, performed according to the instructions for the Multiple Sclerosis Functional Composite.\textsuperscript{14} Patients could use an assistive device as long as this was consistent across visits. The task was performed twice at each visit, and the average value was used. The only prospectively defined secondary outcome measure was the Lower Extremity Manual Muscle Test (LEMMT), using the modified British Medical Research Council scale\textsuperscript{15} and averaging scores for hip flexors, knee flexors and extensors, and ankle dorsiflexors, bilaterally.

Additional measures were collected to allow comparison with the results of previous studies\textsuperscript{1,10}: the Ashworth score for spasticity,\textsuperscript{16} the 12-item Multiple Sclerosis Walking Scale (MSWS-12),\textsuperscript{17} a Subject Global Impression (SGI), and a Clinician Global Impression (CGI). The Ashworth score was averaged across 3 muscle groups bilaterally: hip adductors, knee extensors, and flexors. The SGI, assessed at Visits 1 to 6, asked the patients to rate their impression of the effects of the study medication during the preceding week on their physical well-being, using a 7-point scale (1 = terrible to 7 = delighted). The CGI, assessed once at Visit 6, addressed the supervising clinician's impression of the patient's neurological condition on a 7-point scale (1 = very much improved to 7 = very much worse) relative to screening. At the follow-up visit, Subject and Clinician Summary Questionnaires asked whether it was felt the patient had received active medication and the basis for that impression.

A separate evaluator at each center, blinded to the patient's overall clinical and safety assessments and global scores, performed all functional outcome measurements, and assessments were performed by the same individual at each visit, whenever possible.

Plasma concentration of dalfampridine was determined, for samples obtained at each clinic visit, using a validated liquid chromatographic–tandem mass spectrometric method. Safety was assessed by adverse event monitoring, vital signs, clinical laboratory tests, and electrocardiographic (ECG) measurements.

**Statistical Analysis**

SAS (SAS Institute, Cary, NC) was used for analysis, with \( p \) values of \( \leq 0.05 \) indicating statistical significance. All tests were 2-sided. The prospectively defined primary efficacy analysis was based on all randomized patients who had at least 1 efficacy evaluation during the double-blind treatment period (the modified Intention to Treat, or Analysis Population).

The primary variable, used for demonstration of efficacy, was responder status. A Timed Walk Responder (TWR) was defined prospectively as a patient with a faster walking speed for at least 3 of the first 4 visits during the double-blind treatment period as compared with the maximum speed for any of the 5 off-drug visits (ie, Screening, and Visits 0, 1, 2, and 8). Differences in the proportion of TW Rs between the dalfampridine and placebo groups were analyzed using the Cochran-Mantel-Haenszel test, controlling for center. The T25FW assessments at Visit 7 were used only to evaluate possible changes in efficacy toward the end of the 12-hour interdosing interval.
Based on results from previous studies, a sample size of 92 patients per treatment group would provide approximately 90% power, at an overall significance level of 0.05, to detect a difference between a dalfampridine response rate of 30% and a placebo response rate of 10%. To ensure that at least 184 patients complete the study, approximately 100 patients were planned to be randomized to each group.

An additional analysis, to examine potential interaction between leg strength changes and Timed Walk Response was performed. To maintain an overall alpha level ≤ 0.05, a prospectively defined, stepwise procedure was planned for analyzing the difference from baseline in the LEMMT score; given significance on the primary endpoint, the dalfampridine-treated TWRs were to be compared with the placebo group then, if there was a significant difference between these groups, the dalfampridine-treated Timed Walk Nonresponders (TWNRs) would be compared to the placebo group. Comparisons were performed using an analysis of variance (ANOVA) model, with effects for responder analysis group and center. Baseline score for each patient was the average of all prerandomization scores.

Additional post hoc analyses were performed to compare the observations in this study to those in the previous phase 3 trial, which had incorporated a number of additional prospective analyses, particularly to address the clinical meaningfulness of the newly developed Timed Walk Response criterion. The following variables were evaluated: SGI, CGI, and average change from baseline in the MSWS-12 score during the double-blind treatment period. These were analyzed via an ANOVA with effects for responder status (TWR versus TWNR) and center. The goal of these comparisons was to determine whether the group of patients qualifying as TWRs subjectively registered an improvement in walking related disability, relative to TWNRs.

Results

Figure 2 shows patient disposition and reasons for discontinuation. One of the 240 patients enrolled discontinued before randomization. All 239 randomized patients took at least 1 dose of investigational drug and were included in the safety population. Two patients did not complete any efficacy assessments and were excluded from the analysis population of 237 patients (118 placebo, 119 dalfampridine). Treatment groups were comparable (Table 1). Only 1 patient in each group was considered noncompliant.

The number of patients who met the responder criterion was 51 of 119 (42.9%) in the dalfampridine-treated group, and 11 of 118 (9.3%) in the placebo-treated group (p < 0.0001; Mantel-Haenszel odds ratio, 8.14; 95% confidence interval [CI], 3.73–17.74). Thus, the number needed to treat to achieve response is approximately 3.

The average change from baseline in walking speed for the dalfampridine-treated TWRs during the efficacy analysis period (Visits 3–6) was 24.7% (95% CI, 21.0–28.4%) or 0.51 ft/s (95% CI, 0.43–0.59) compared to change in the placebo group of 7.7% (95% CI, 4.4–11.0%) or 0.17 ft/s (95% CI, 0.10–0.23). The dalfampridine-treated TWNRs showed no difference in mean response from the placebo group; the average change during treatment was 6.0% (95% CI, 2.2–9.7%) or 0.12 ft/s (95% CI, 0.05–0.19). The increase in walking speed among dalfampridine-treated TWRs was maintained across the double-blind treatment and was reversed with treatment discontinuation (Fig 3).

The improvement from baseline walking speed among dalfampridine TWRs at the first evaluation at Visit 7 was 25.7% (95% CI, 19.8–31.7%). The mean improvement in walking speed among dalfampridine TWRs at Visit 7 for assessment time windows of 9 to 10 hours, 10 to 11 hours, and 11 to 12 hours postdose was 25.5%, 25.3%, and 20.1%, respectively.

The average changes from baseline in MSWS-12 score during the double-blind treatment period were −6.04 (95% CI, −9.57 to −2.52) for TWRs compared to 0.85 (95% CI −0.72 to 2.43) for TWNRs, independent of treatment assignment, indicating a reduction in self-assessed ambulatory disability among TWRs (nominal p < 0.001). All 12 items in the test showed a mean reduced disability score for the TWR compared to the TWNR group, indicating improvement across a wide range of daily life activities related to walking. TWRs also had more positive SGI scores compared to TWNRs (mean score, 4.76 vs 4.21; nominal p < 0.001) and were rated more improved than TWNRs on the CGI score (mean score, 3.38 vs 3.75; nominal p < 0.001).

The average improvement in the LEMMT score for the dalfampridine TWRs during the double-blind period was 0.145U compared to 0.042U for the placebo group (nominal p = 0.028). The mean improvement of 0.048U for dalfampridine TWNRs was not significantly different from either the dalfampridine TWRs or the placebo group.

Additional Efficacy Analysis

In addition to the planned response analysis, other direct treatment group comparisons were also made, showing...
that the dalfampridine-treated group was statistically significantly superior to placebo with respect to average percentage change from baseline in walking speed (13.99% vs 7.67%, \(p = 0.007\)), average change from baseline in Ashworth score (\(-0.18\) vs \(-0.06\), \(p = 0.015\)), average change from baseline in the MSWS-12 score (\(-2.62\) vs \(-0.73\), \(p = 0.021\)), and CGI at the end of the double-blind period (3.52 vs 3.79, \(p = 0.002\)). The average change in SGI score also favored the dalfampridine-treated group but was not statistically significant.

**Study Blinding**

In the Subject Summary Questionnaire, 45% of dalfampridine-treated patients and 45% of placebo-treated patients correctly assessed treatment assignment. The Clinician Summary Questionnaire responses showed that clinicians, at the end of the study, correctly identified drug assignment for 38% of dalfampridine-treated patients and 35% of placebo-treated patients, suggesting that there was no significant unblinding of patients or clinicians by side effects.

**Baseline Characteristics of Dalfampridine-Treated TWRs**

The responder analysis groups (dalfampridine TWRs, dalfampridine TWNRs, and placebo patients) appeared comparable (see Table 1), including clinical characteristics such as the Expanded Disability Status Scale score,\(^{18}\) disease course, and baseline medications. There was a difference in gender distribution between dalfampridine and placebo groups, but there was no association between gender and response on the primary endpoint, and this imbalance did not affect the efficacy outcome, as determined in a sensitivity analysis.

**Safety: Adverse Events**

Eight patients, 4 in each treatment group (3.4% placebo, 3.3% dalfampridine), were withdrawn from the study due to adverse events. The events (MedDRA [Medical
Dictionary for Regulatory Activities] terms) in the placebo group were ventricular extrasystoles, coordination abnormal, complex partial seizure, and gastroesophageal reflux disease. The events in the dalfampridine group were hypotension, headache, patella fracture, and neurological symptoms (verbatim "neurological status deterioration"). The incidence of treatment-emergent adverse events is summarized in Table 2. Eight patients, 3 (2.5%) in
the placebo group and 5 (4.2%) in the dalfampridine-treated group, experienced ≥1 serious adverse event (SAE). The SAEs in the placebo group were urinary tract infection (UTI), complex partial seizure, and a combination of gastroesophageal reflux disease and chest discomfort. Those in the dalfampridine group were pneumonia, cellulitis, pyelonephritis, patella fracture, coronary artery disease, and a combination of cholelithiasis and syncope.

Table 2 shows differences between treatment groups in the frequency of individual adverse events. The largest proportional differences were found among nervous system events, including insomnia, headache, dizziness, nausea, back pain, and balance disorder. The majority of these events were mild or moderate in intensity and transient, not leading to study discontinuation. There were no notable differences between treatment groups with respect to laboratory values, vital signs, or ECG findings.

**Plasma Dalfampridine Concentrations**

The mean plasma concentrations of dalfampridine in the dalfampridine-treated group were between 28.5 and 30.2 ng/ml at each of the first 4 double-blind visits (standard deviation [SD], 11.2–13.3 ng/ml; range, 0–87.3 ng/ml). The mean plasma concentration at Visit 7, from samples obtained at the time of the first of 3 efficacy assessments (8–10 hours postdose) was 21.2 ± 9.7 (range, 0–56.4 ng/ml). There was no clinically meaningful difference in plasma concentration between dalfampridine-treated TWRs and TWRs. The mean (±SD) plasma concentrations across all samples collected during

---

**TABLE 2: Summary of AEs and Most Frequent AEs (MedDRA Terms)**

<table>
<thead>
<tr>
<th>Patients</th>
<th>Placebo, n = 119</th>
<th>Dalfampridine, n = 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE, No. (%)</td>
<td>79 (66.4)</td>
<td>103 (85.8)</td>
</tr>
<tr>
<td>Mild</td>
<td>36 (30.3)</td>
<td>39 (32.5)</td>
</tr>
<tr>
<td>Moderate</td>
<td>36 (30.3)</td>
<td>53 (44.2)</td>
</tr>
<tr>
<td>Severe</td>
<td>7 (5.9)</td>
<td>11 (9.2)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>3 (2.5)</td>
<td>5 (4.2)</td>
</tr>
<tr>
<td>Possibly or probably treatment-related AE</td>
<td>15 (12.6)</td>
<td>25 (20.8)</td>
</tr>
</tbody>
</table>

**Most frequent AEs**

- **Urinary tract infection**: 10 (8.4) | 21 (17.5)
- **Fall**: 20 (16.8) | 14 (11.7)
- **Insomnia**: 2 (1.7) | 12 (10.0)
- **Headache**: 1 (0.8) | 11 (9.2)
- **Asthenia**: 5 (4.2) | 10 (8.3)
- **Dizziness**: 1 (0.8) | 10 (8.3)
- **Nausea**: 1 (0.8) | 10 (8.3)
- **Back pain**: 3 (2.5) | 7 (5.8)
- **Balance disorder**: 2 (1.7) | 7 (5.8)
- **Upper respiratory tract infection**: 8 (6.7) | 7 (5.8)
- **Arthralgia**: 5 (4.2) | 6 (5.0)
- **Nasopharyngitis**: 5 (4.2) | 6 (5.0)
- **Paresthesia**: 2 (1.7) | 6 (5.0)

*Occurring in >5% of fampridine-treated patients.

AE = adverse event; MedDRA = Medical Dictionary for Regulatory Activities.
An earlier study\textsuperscript{10} showed that consistent improvement in ambulatory dysfunction in MS is a central feature of MS and its progression.\textsuperscript{18,19} The primary efficacy outcome was a response rate analysis, comparing between the dalfampridine- and placebo-treated groups the proportion of patients who experienced a consistent improvement in walking speed during treatment. An earlier study\textsuperscript{10} showed that consistent improvement in walking speed provided a response criterion that was more specific for treatment-related change than an arbitrary threshold for average magnitude of improvement.

Patients experiencing faster walking speeds for the majority of visits while on study medication compared to the fastest speed during the off-treatment period were defined as TWRs. For dalfampridine-treated patients, 42.9% met this criterion, compared to 9.3% in the placebo-treated group, and this difference was both highly significant and similar to the results of previous trials.\textsuperscript{1,10}

Responsiveness to treatment may be related to the proposed mechanism of action, improvement of conduction in demyelinated pathways via blockade of voltage-dependent potassium channels.\textsuperscript{2,3} Not all patients would be expected to have axons relevant to walking that are susceptible to treatment. The Timed Walk Response criterion was shown in earlier studies to identify patients with consistently increased walking speed during treatment who, as a group, appreciated improvement in their self-assessed walking-related disabilities on the MSWS-12 scale.\textsuperscript{1,10} By identifying such a group of patients, this form of analysis can give a realistic estimate of the number needed to treat. Comparing the mean walking speed between treatment groups, although showing statistical significance, gives no equivalent sense of the clinical meaningfulness of the treatment effect or the number needed to treat.

The average improvement in walking speed during the double-blind efficacy period was 24.7% for the dalfampridine-treated TWRs compared to 7.7% for the placebo group. This improvement was maintained over the 9 weeks of treatment and was similar to that observed in 2 previous studies involving 14 weeks of treatment.\textsuperscript{1,10} Additional sensitivity analysis showed that this conclusion was not affected by the exclusion of 1 patient from each group from the analysis population for lack of data.

Although there was no prospective plan to evaluate the MSWS-12, SGI, and CGI scores other than integrated analysis across studies, the changes observed in these measures were similar to those seen in the previous trials.\textsuperscript{1,10} There were improvements in all 3 measures in TWRs compared to TWNRs, consistent with evaluation of clinical meaning of the Timed Walk Response criterion performed earlier.\textsuperscript{10}

There was no indication in this or in the preceding studies\textsuperscript{1,10} of any difference between dalfampridine-treated TWRs and TWNRs with respect to any other measure collected within the study. The susceptibility of individual patients to this treatment is likely to be related to the particular distribution and physiological characteristics of lesions within the nervous system. The response criterion is a statistical tool rather than a biological assay, and although the criterion produces an all-or-none classification, this does not imply an all-or-none biological phenomenon.

Another goal of the study was to examine efficacy across the dosing period. This was addressed by requiring 3 evaluations of walking speed at Visit 7 (each separated by 1 hour) between 8 and 12 hours after the last dose of study medication. This showed that the improvement in walking speed among dalfampridine-treated TWRs was not significantly diminished toward the end of the interdosing period compared to assessments made during the normal course of the study. Although the plasma concentration of dalfampridine was reduced approximately 25% at the first assessment at Visit 7, there was no reduction in mean increase in walking speed from baseline (25.7% compared to 24.7% for the average of Visits 3–6). Decreases in central nervous system concentrations of dalfampridine may be delayed relative to the decline in plasma levels.\textsuperscript{20} Walking speed improvement over baseline did decline for measurements at 11 to 12 hours postdose (to a mean of 20.1%).

The most frequent treatment-emergent adverse events in both the treatment groups were medical conditions affecting people with MS, and the majority of these were mild or moderate in intensity. UTI, insomnia, headache, asthenia, dizziness, nausea, back pain, balance disorder, and paresthesia were each reported at rates >50% higher in the drug group. This may represent a treatment-related increase, and similar disparities (>50% increase) were seen in the previous phase 3 study\textsuperscript{1} for insomnia, back pain, and balance disorder. However, there were no differences between treatment groups in the incidence of UTI, headache, or asthenia in that trial. Four patients (3%) in each treatment group discontinued due to adverse events. The only seizure-related event occurred in the placebo-treated group (presumed complex
partial seizure). 4-Aminopyridine is known to promote seizure events in overdose, and seizures were seen in 4 patients at higher doses in earlier controlled studies of extended-release dalfampridine. The incidence of seizure-related events at 10mg twice daily has been similar to placebo in controlled trials of extended-release dalfampridine, with 1 event in the placebo group in this study and 1 in the dalfampridine group in the previous study. The incidence of seizure in open-label extension studies at this dose to date has been similar to background rates of first seizure of approximately 0.35 per 100 patient-years.

To conclude, a significantly higher proportion of dalfampridine-treated patients showed consistently improved walking speed, maintained over the interdosing period of 12 hours. This confirmed the results of the first phase 3 trial, showing that treatment with dalfampridine produces clinically meaningful improvement in walking ability in a subgroup of MS patients. These 2 studies suggest that dalfampridine represents a potentially useful and novel class of therapy for MS, as a modulator of neural function that may be complementary to existing immunomodulatory therapies.

Acknowledgments
The study was sponsored by Acorda Therapeutics, Inc. and supported by a grant from the Stony Brook Research Foundation (L.B.K.).

Authorship
L.N.M. was responsible for statistical analysis.

Potential Conflicts of Interest
R.C., L.N.M., and A.R.B. are employed by Acorda Therapeutics and own stock in the company. A.D.G., T.R.B., K.R.E., L.B.K., and R.T.S. have received funds from Acorda Therapeutics. A.D.G. has received honoraria and travel reimbursement from Actelion, Avanir, Bayer, Biogen-Idec, EMD-Serono, Genentech, Genzyme, Pfizer, and Teva.

Appendix

**MS-F204 Study Investigators**

Mark Agius, MD (University of California, Davis, CA); Barry G. W. Arnason, MD (University of Chicago, Chicago, IL); Francois A. Bethoux, MD (Cleveland Clinic Foundation, Cleveland, OH); Christopher T. Bever, Jr, MD (University of Maryland at Baltimore, Baltimore, MD); Theodore R. Brown, MD (Evergreen Hospital Medical Center, Kirkland, WA); Ann Camac, MD (Lahey Clinic, Lexington, MA); Joanna A. Cooper, MD (East Bay Physicians Medical Group, Berkeley, CA); Warren F. Chumley, MD (Associates in Neurology, Lexington, KY); Anne Cross, MD (Washington University School of Medicine, St Louis, MO); Dennis W. Dietrich, MD (Advanced Neurology Specialists, Great Falls, MT); Ralph T. Dunnigan, MD (Center for Neurological Services, Bismarck, ND); Keith Edwards, MD (Neurological Research Center Inc., Bennington, VT); Mitchell Freedman, MD (Raleigh Neurology Associates, Raleigh, NC); Jeffrey S. Gitt, DO (HOPE Research Institute, Phoenix, AZ); Machteld Hillen, MD (University of Medicine and Dentistry of New Jersey, Newark, NJ); Douglas R. Jeffery, MD, PhD (Wake Forest University Health Sciences, Winston-Salem, NC); Norman J. Kachuck, MD (University of Southern California Keck School of Medicine, Los Angeles, CA); Bhupendra O. Khatri, MD (Center for Neurological Disorders, Milwaukee, WI); Michael D. Kaufman, MD (Carolinas Medical Center, Charlotte, NC); Omar Khan, MD (Wayne State University, Detroit, MD); Kirin Kresa-Reahl, MD (Capitol Neurology, PPLC, Charleston, WV); Lauren B. Krupp, MD (Stony Brook University Medical Center, Stony Brook, NY); Thomas P. Leist, MD, PhD (Thomas Jefferson University, Philadelphia, PA); Fred D. Lublin, MD (Mount Sinai School of Medicine, New York, NY); Michele K. Mass, MD (Oregon Health Sciences University, Portland, OR); David Mattson, MD, PhD (Indiana University Medical Center, Indianapolis, IN); Daniel McGowan, MD (University of Calgary and Foothills Hospital, Calgary, Alberta, Canada); Steven Moon, MD (Neurological Associates, PLC, Fayetteville, AR); Colleen O’Connell, MD (Stan Cassidy Centre for Rehabilitation, Fredericton, New Brunswick, Canada); Joel J. Oger, MD (University of British Columbia, Vancouver, BC); Hillel Panitch, MD (Fletcher Allen Health Care, Burlington, VT); Mary A. Picone, MD (Gimbel Multiple Sclerosis Center, Teaneck, NJ); Jana Preiningerova, MD (Yale Multiple Sclerosis Center, New Haven, CT); Kotttil W. Rammohan, MD (Ohio State University, Columbus, OH); Randall T. Schapiro, MD (Schapiro Center for Multiple Sclerosis, Golden Valley, MN); Steven R. Schwid, MD (University of Rochester Medical Center, Rochester, NY); Christine Short, MD (Nova Scotia Rehabilitation Centre, Halifax, Nova Scotia, Canada); Ben W. Thrower, MD (Shepherd Center, Atlanta, GA); Mark Tullman, MD (Columbia Multiple Sclerosis Clinical Care Center, New York, NY); Bianca Weinstock-Guttman, MD (Jacobs Neurological Institute, Buffalo, NY); Daniel R. Wynn, MD (Consultants in Neurology, Ltd., Northbrook, IL); and Timothy L. Vollmer, MD (Barrow Neurological Institute, Phoenix, AZ).

*Screened but did not enroll patients.
References


