

# Sustained-release oral fampridine in multiple sclerosis: a randomised, double-blind, controlled trial

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## Summary

**Background** Clinical studies suggested that fampridine (4-aminopyridine) improves motor function in people with multiple sclerosis. This phase III study assessed efficacy and safety of oral, sustained-release fampridine in people with ambulatory deficits due to multiple sclerosis.

**Methods** We undertook a randomised, multicentre, double-blind, controlled phase III trial. We randomly assigned 301 patients with any type of multiple sclerosis to 14 weeks of treatment with either fampridine (10 mg twice daily; n=229) or placebo (n=72), using a computer-generated sequence stratified by centre. We used consistent improvement on timed 25-foot walk to define response, with proportion of timed walk responders in each treatment group as the primary outcome. We used the 12-item multiple sclerosis walking scale to validate the clinical significance of the response criterion. Efficacy analyses were based on a modified intention-to-treat population (n=296), which included all patients with any post-treatment efficacy data. The study is registered with ClinicalTrials.gov, number NCT00127530.

**Findings** The proportion of timed walk responders was higher in the fampridine group (78/224 or 35%) than in the placebo group (6/72 or 8%;  $p < 0.0001$ ). Improvement in walking speed in fampridine-treated timed walk responders, which was maintained throughout the treatment period, was 25.2% (95% CI 21.5% to 28.8%) and 4.7% (1.0% to 8.4%) in the placebo group. Timed walk responders showed greater improvement in 12-item multiple sclerosis walking scale scores ( $-6.84$ , 95% CI  $-9.65$  to  $-4.02$ ) than timed walk non-responders ( $0.05$ ,  $-1.48$  to  $1.57$ ;  $p = 0.0002$ ). Safety data were consistent with previous studies.

**Interpretation** Fampridine improved walking ability in some people with multiple sclerosis. This improvement was associated with a reduction of patients' reported ambulatory disability, and is a clinically meaningful therapeutic benefit.

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## Introduction

Fampridine (4-aminopyridine) is a potassium-channel blocker that has been investigated in various neurological conditions.<sup>1,2</sup> Studies in people with multiple sclerosis have indicated that treatment with fampridine is associated with improvements in visual function, strength, ambulation, fatigue, and endurance.<sup>3-6</sup> An independent, systematic review by the Cochrane collaboration of published research in 2002 looked at six main randomised controlled trials, five of which assessed fampridine and one amifampridine (3,4-diaminopyridine), together involving 198 participants.<sup>7</sup> The investigators suggested that no conclusion can be made about safety or efficacy of aminopyridines for treatment of multiple sclerosis symptoms. They expressed particular concern about the small size of these studies and the potential for publication bias. Two other studies focused on walking ability as the primary endpoint,<sup>8,9</sup> with a sustained-release, oral tablet formulation of fampridine, fampridine-SR, which was developed to maintain stable plasma concentrations of the drug when given twice daily.<sup>10,11</sup> Ambulatory impairment is a key feature of multiple sclerosis and a major factor to

assess progression of the disease.<sup>12-14</sup> We aimed to provide further evidence for safety and efficacy of sustained-release fampridine in people with multiple sclerosis for ambulation and leg strength.

## Methods

### Study participants

Eligible patients were aged 18–70 years, with clinically defined multiple sclerosis,<sup>15</sup> able to complete two trials of the timed 25-foot walk (T25FW) in an average time of 8–45 s at screening. Patients were excluded if they had onset of multiple sclerosis exacerbation within 60 days of screening, a history of seizures or evidence of epileptiform activity on a screening electroencephalogram, or any condition that would interfere with the conduct or interpretation of the study. We set additional restrictions on changes in concomitant medications to avoid related changes in multiple sclerosis symptoms during the trial.

### Study design

This study was a randomised, double-blind, placebo-controlled trial. Patients underwent screening without receiving any study medication and eligible

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patients returned 1 week later (visit 0, figure 1). Patients then entered a 2-week, single-blind, placebo run-in period; visit 1 occurred at the beginning of week 2 of placebo run-in and visit 2 at the end of week 2. Patients were instructed to take one tablet (supplied in appropriate quantities at each clinic visit) every 12 h during the treatment phase.

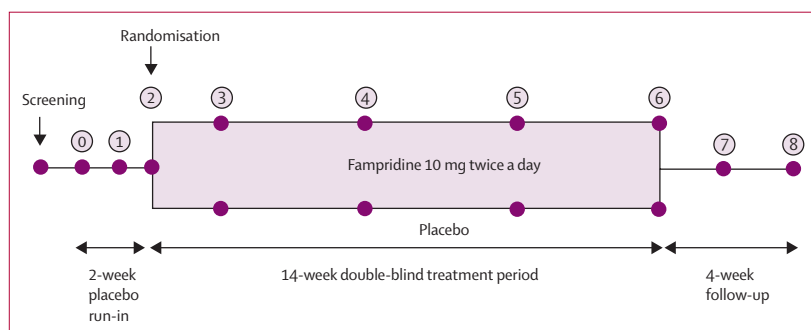
At visit 2, patients were randomly assigned to fampridine (10 mg twice daily) or to placebo (tablets, twice daily) at a ratio of 3:1, with a predetermined, computer-generated randomisation schedule, blocked and stratified by treatment site and prenumbered treatment kits. We used independent statistical, packaging, and distribution contractors to maintain the blind for all other personnel. After 2 weeks, patients returned for the first double-blind examination (visit 3). Patients then returned every 4 weeks for examination (visits 4–6). At the end of the 14-week double-blind treatment period (visit 6), patients began a 4-week period of no treatment, returning for follow-up assessments at 2-week intervals (visits 7 and 8).

33 centres in the USA and Canada participated in this study. The trial was done in accordance with the Declaration of Helsinki and its subsequent amendments, Good Clinical Practice and applicable regulatory requirements. The research protocol was approved by the relevant institutional review boards or ethics committees, and all participants gave written informed consent.

### Outcome measures

The primary outcome measure of efficacy—response to treatment—was based on changes in walking speed (in feet per second), as measured by the T25FW, done according to the instructions for the multiple sclerosis functional composite.<sup>16</sup> Patients were allowed to use an assistive device as long as it was consistently used across visits. The task was done twice at each visit, allowing a maximum of 5-min rest between tests, and we used the average value for analysis. Two secondary outcome measures of efficacy were the Ashworth score for spasticity<sup>17</sup> and a lower extremity manual muscle test (LEMMT) done at each visit.

We used the 12-item multiple sclerosis walking scale (MSWS-12),<sup>14</sup> a rating scale that captures patients' perspectives on their ambulatory disability, as the primary measure to validate the clinical significance of the timed-walk response criterion and assessed it at all visits except for visit 1. Secondary validation variables were a subject global impression (SGI) and a clinician global impression (CGI). We averaged the Ashworth score across three muscle groups bilaterally: hip adductors, knee extensors, and knee flexors. The LEMMT measured strength in four muscle groups bilaterally (hip flexors, knee flexors and extensors, and ankle dorsiflexors) with the modified British Medical Research Council scale.<sup>18</sup> The SGI, assessed at visits 1–6, asked the patients to rate their perception of the effects of the study medication



**Figure 1: Study schedule and design**

After a screening visit for assessment of eligibility, patients returned at visit 0 and received single-blind placebo medication for 2 weeks. At visit 2, patients were randomly assigned to fampridine or placebo treatment, and returned for four visits (visits 3–6) over the course of the 14 weeks of double-blind treatment. Active treatment discontinued at visit 6, and patients returned 2 and 4 weeks after treatment for follow-up visits 7 and 8. Visit numbers are circled.

during the preceding week on their physical wellbeing with a 7-point scale (1=terrible to 7=delighted). The CGI, assessed once at visit 6, addressed the supervising clinician's judgment of the patient's neurological condition on a 7-point scale (1=very much improved to 7=very much worse) relative to the screening visit. Patient and clinician summary questionnaires were completed at the final follow-up visit to assess the views of the patient and clinician regarding whether the patient had received active medication.

A separate specifically trained evaluator, usually a physical therapist, at each centre—unaware of the patient's overall clinical and safety assessments, and CGI and SGI scores—did all functional outcome measurements. Assessments were done by the same individual at every visit whenever possible.

We measured plasma concentration of fampridine for individual samples obtained at each clinic visit, with a validated liquid chromatographic-mass spectrometric-mass spectrometric method at the central laboratory. We assessed safety by monitoring adverse events, vital signs, clinical laboratory tests, and electrocardiogram (ECG) measurements.

An independent data safety monitoring committee was empowered to review unblinding safety data during the study and to make recommendations to the sponsor regarding the conduct of the trial.

### Statistical analysis

We used SAS version 8.2 for data analysis, with p values of 0.05 or less indicating statistical significance. All tests were two-sided. We based the primary efficacy analysis on all randomised patients who had at least one efficacy assessment of T25FW and MSWS-12 during the double-blind treatment period (intention-to-treat population).

The primary efficacy variable was responder status, based on consistency of walking speed improvement. A timed walk responder was defined as a patient with a faster walking speed for at least three of the four visits during the double-blind treatment period than the

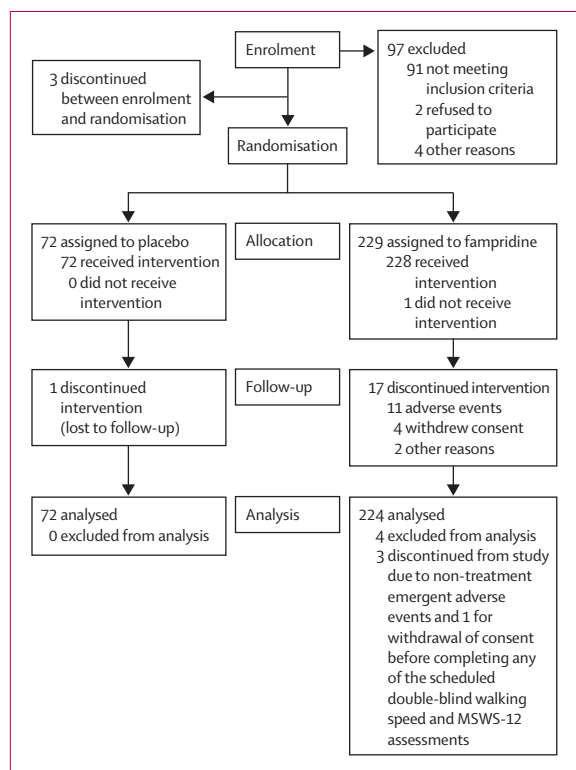


Figure 2: Trial profile

maximum speed for any of the first five off-drug visits (four before double-blind treatment and one at 2 weeks after discontinuation of treatment—ie, screening and visits 0, 1, 2, and 7). Missed assessments during treatment were assumed to fall within the off-treatment range (ie, the primary efficacy endpoint was conservatively analysed without imputation for missing data). We analysed differences in the proportion of responders between fampridine and placebo groups with the Cochran-Mantel-Haenszel test, controlling for centre.

We analysed the average change from baseline in the MSWS-12 score during the double-blind treatment period for responder status (timed walk responders vs non-responders) using an ANOVA model, with effects for responder status and centre. We did similar analyses for the secondary subjective validation variables, SGI and CGI.

For changes from baseline in walking speed and each of the secondary objective variables, we analysed differences between the three responder analysis groups (placebo, fampridine-treated timed walk non-responders, and fampridine-treated timed walk responders) with *t* tests of the least-squares means, using the mean square error using an ANOVA model with effects for responder analysis group and centre. To maintain the overall alpha level, we did a prospectively defined, stepwise procedure for the secondary variables. For the objective secondary efficacy variables analysed longitudinally, we imputed the average post-baseline value for any missing values during the double-blind period. Baseline for the quantitative

	Placebo (N=72)	Fampridine		
		Total (N=228)	Responders (N=78)	Non-responders (N=150)
Age (years) (range)	50.9 (8.9) (34–69)	51.5 (8.7) (26–70)	51.4 (8.7) (31–70)	51.6 (8.8) (26–70)
Sex				
Male	29 (40%)	66 (29%)	19 (24%)	47 (31%)
Female	43 (60%)	162 (71%)	59 (76%)	103 (69%)
Race				
White	67 (93%)	211 (93%)	71 (91%)	140 (93%)
Black	3 (4%)	10 (4%)	4 (5%)	4 (4%)
Hispanic	1 (1%)	3 (1%)	0	3 (2%)
Asian/Pacific islander	1 (1%)	3 (1%)	2 (3%)	1 (1%)
Other	0	1 (0.4%)	1 (1%)	0
MS course				
Relapsing remitting	21 (29%)	62 (27%)	15 (19%)	47 (31%)
Primary progressive	14 (19%)	31 (14%)	11 (14%)	20 (13%)
Secondary progressive	35 (49%)	125 (55%)	48 (62%)	77 (51%)
Progressive relapsing	2 (3%)	10 (4%)	4 (5%)	6 (4%)
Immunomodulator treatment*	51 (71%)	151 (66%)	51 (65%)	100 (67%)
MS duration (years) (range)	12.7 (8.21) (1.4–37.7)	13.4 (8.29) (0.4–41.7)	14.1 (8.36) (0.7–41.7)	13.1 (8.26) (0.4–38.1)
EDSS score (range)	5.8 (1.1) (2.5–6.5)	5.8 (1.0) (2.5–7.0)	5.8 (1.0) (2.5–7.0)	5.7 (1.0) (3.0–7.0)
Timed 25-foot walk speed (feet/s)	2.1 (0.7)	2.1 (0.7)	2.1 (0.7)	2.0 (0.8)
LEMMT score	4.0 (0.7)	4.1 (0.6)	4.0 (0.5)	4.1 (0.6)
Ashworth score	1.0 (0.7)	1.0 (0.7)	0.9 (0.6)	0.9 (0.7)
MSWS-12 score	68.5 (22.3)	70.7 (18.6)	70.3 (18.6)	70.1 (19.9)
SGI score†	4.7 (0.9)	4.6 (0.9)*	4.6 (0.9)*	4.6 (0.9)*

Data are mean (SD) or number (%). EDSS=expanded disability status scale. MS=multiple sclerosis. LEMMT=lower extremity manual muscle test. MSWS-12=12-item multiple sclerosis walking scale. SGI=subject global impression. Safety population included 300 randomised patients. \*Concomitant treatment with an interferon or glatiramer acetate. †SGI data were not available for two patients, one in the responder group and one in the non-responder group.

Table 1: Demographics and baseline characteristics

outcome variables was the average of all pre-randomisation values (screening to visit 2).

On the basis of the results from a study,<sup>9</sup> 180 patients treated with fampridine and 60 patients on placebo provide a power of about 90% for the primary outcomes (response rate, maintenance of effect, and clinical validation).

### Role of the funding source

The sponsor was responsible for data collection and statistical analysis, and collaborated with the authors in study design, data interpretation, writing of the report,

and in the decision to submit the paper for publication. After database lock and study unblinding, the corresponding author had full access to all the data in the study. The corresponding author had the final responsibility for the decision to submit for publication.

## Results

Figure 2 shows patient disposition and reasons for discontinuation. Of the 301 randomised patients, one did not take the double-blind medication and was excluded from the safety analysis. Four patients discontinued before completing any efficacy measurements during the double-blind period and were excluded from the intention-to-treat population. Treatment groups were comparable for baseline demographics, disease characteristics, and efficacy variables (table 1). Compliance with study medication during the trial was more than 97% for both treatment groups.

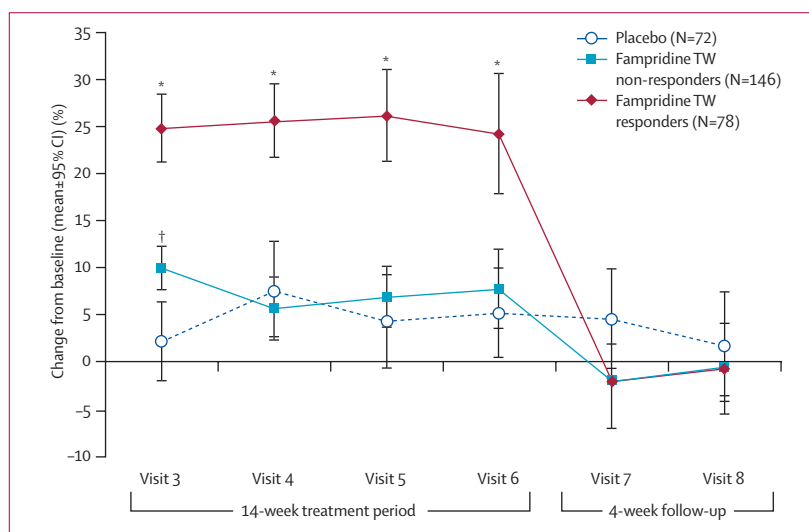
The number of patients who met the responder criterion—ie, timed walk responders—was 78 of 224 (35%) in the fampridine-treated group and 6 of 72 (8%) in the placebo group ( $p < 0.0001$ ; Mantel-Haenszel odds ratio [OR] 4.75; 95% CI 2.08 to 10.86).

The average change from baseline in walking speed for the fampridine-treated timed walk responders during the treatment period was 25.2% (95% CI 21.5% to 28.8%) or 0.51 feet/s (0.41 to 0.61), and 4.7% (1.0% to 8.4%) or 0.10 feet/s (0.03 to 0.17) in the placebo group. The increase in walking speed in fampridine-treated responders was maintained during 14 weeks of treatment (figure 3). For the fampridine-treated timed walk non-responders, the average change during treatment was 7.5% (5.0% to 10.0%) or 0.16 feet/s (0.11 to 0.21). Increase in walking speed in non-responders was small but significant compared with that in the placebo group at the earliest double-blind treatment visit, but no difference existed at any subsequent visit (figure 3).

Average changes from baseline in MSWS-12 score during the treatment period were  $-6.84$  ( $-9.65$  to  $-4.02$ ) for timed walk responders and  $0.05$  ( $-1.48$  to  $1.57$ ) for non-responders, independent of treatment assignment ( $p = 0.0002$ ), indicating a reduced self-assessed ambulation-related disability in timed walk responders. All 12 items in the test showed a reduced mean disability score in the responder group compared with that in the non-responder group.

Patients identified as timed walk responders also had more positive SGI scores than had non-responders (mean score 4.88 vs 4.43,  $p = 0.001$ ; median average score 5.00 vs 4.25) and were rated more improved than were non-responders on the CGI score (mean score 3.28 vs 3.74,  $p < 0.0001$ , median score 3 vs 4).

The average improvement in the LEMMT score for the fampridine-treated timed walk responders during the double-blind period was 0.18 compared with 0.04 for the placebo group ( $p = 0.0002$ ). The fampridine-treated



**Figure 3: Percent change in walking speed at each visit after randomisation**

The fampridine-treated timed walk responders showed a sustained improvement during the treatment period that was completely reversed at 2-week and 4-week follow-up visits. The fampridine-treated timed walk non-responders showed a significant improvement compared with the placebo group only for visit 3 (2 weeks after randomisation). TW=timed walk. \*Means fampridine TW responders are greater than placebo and fampridine TW non-responders ( $p < 0.001$ ). †Means fampridine TW non-responders are greater than placebo only ( $p < 0.001$ ).

non-responder group also showed improved leg strength compared with the placebo group (0.11,  $p = 0.046$ ). The average Ashworth score improved in the fampridine-treated timed walk responder and non-responder groups more than that in the placebo group, but this difference was not significant for the responder group and not eligible for testing under the prospectively defined sequential analysis plan.

In addition to the planned responder analysis, the fampridine-treated group was compared retrospectively with the placebo group. The fampridine-treated group showed a greater improvement than the placebo group as measured by all three objective outcome measures: average change from baseline in walking speed (nominal  $p = 0.0004$ ), LEMMT (nominal  $p = 0.0029$ ), and Ashworth score (nominal  $p = 0.0210$ ). No significant differences existed between any of the responder analysis groups for any of the three objective variables at the two follow-up visits.

In the subject summary questionnaire, 46% of fampridine-treated and 36% of placebo-treated individuals correctly assessed their treatment assignment. Of the fampridine-treated patients, 27% of those who thought they had received active medication based their conclusion at least in part on adverse effects, whereas 92% attributed their conclusion to perceived changes in multiple sclerosis symptoms. The clinician summary questionnaire responses showed that clinicians, at the end of the study, correctly identified drug assignment for 38% of fampridine-treated and 33% of placebo-treated individuals, suggesting no significant unblinding due to side-effects.

	Placebo (N=72)	Fampridine (N= 228)
Any adverse event	58 (81%)	191 (84%)
Mild	16 (22%)	59 (26%)
Moderate	35 (49%)	98 (43%)
Severe	7 (10%)	34 (15%)
Serious adverse events	0	16 (7%)
Possibly or probably treatment-related adverse events	19 (26%)	62 (27%)
Possibly or probably treatment-related serious adverse events	0	2 (1%)
Most frequent adverse events*		
Fall	11 (15%)	36 (16%)
Urinary tract infection	10 (14%)	31 (14%)
Dizziness	4 (6%)	19 (8%)
Insomnia	3 (4%)	19 (8%)
Fatigue	2 (3%)	14 (6%)
Nausea	3 (4%)	14 (6%)
Upper respiratory tract infection	7 (10%)	14 (6%)
Asthenia	4 (6%)	13 (6%)
Back pain	0	13 (6%)
Balance disorder	2 (3%)	13 (6%)
Headache	4 (6%)	13 (6%)

Data are number (%). \*Occurring in more than 5% of fampridine-treated patients.

**Table 2: Adverse events (MedDRA terms)**

The responder analysis groups (fampridine-treated responders, fampridine-treated non-responders, and patients on placebo) seemed comparable at baseline (table 1) for all efficacy and demographic variables, baseline multiple sclerosis symptoms (including temperature sensitivity and cerebellar involvement), and other clinical characteristics such as expanded disability status scale (EDSS) score, disease course, and baseline medications. Most patients were on stable immunomodulator therapy; these patients did not differ between treatment or responder groups, although they differed, as expected, in multiple sclerosis types. Distribution between sexes differed slightly between fampridine and placebo groups; however, there was no association between sex and response on the primary endpoint, and this imbalance did not affect the efficacy outcome.

Table 2 summarises the frequency of treatment-emergent adverse events. 11 patients in the fampridine group (5%) were withdrawn from the study due to adverse events. In eight of them, adverse events (sepsis, ankle fracture, balance disorder, confusional state, dizziness, headache, and anxiety) began during the double-blind treatment period, whereas in the other three the events began before the double-blind period. No patients died during the study; one patient died one week after study completion (five weeks after the last dose of fampridine) of ischaemic and hypertensive heart disease, which was considered by the investigator to be unrelated

to study medication. Of the 16 patients who discontinued for any reason during the double-blind phase, one was in the placebo group and 15 were fampridine-treated timed walk non-responders.

16 patients in the fampridine-treated group (7%) had one or more serious adverse events during the double-blind period, the most common being urinary tract infection (n=2) and multiple sclerosis exacerbation (two events in one patient). Only two serious adverse events were possibly or probably related to treatment. One was severe anxiety in a patient who had been taking diazepam as required for anxiety and insomnia before the study. Study drug was withheld and the anxiety resolved, but reappeared on re-challenge. The other was sepsis secondary to community-acquired pneumonia in a patient who was also being treated for urinary tract infection. During this event, a focal seizure appeared, involving the right extremity, and this was judged as possibly related to treatment.

Some patients had clinically significant changes during treatment for laboratory values, vital signs, or ECG findings, but there were no clear trends within or differences between treatment groups in type or frequency of clinically significant results.

The mean plasma concentrations of fampridine in the fampridine-treated group were 27.6–29.2 ng/mL at each double-blind visit with SD of 11.5–12.3 ng/mL, and an overall range of 0–66.8 ng/mL. The time of plasma sampling, relative to the time of the previous dose of study medication, was freely variable with the schedules of clinic visits.

## Discussion

Our aim was to assess the efficacy and safety of sustained-release oral fampridine to treat ambulatory dysfunction in multiple sclerosis. At present, no pharmaceutical treatment exists for this disability. The primary efficacy outcome was based on walking speed, measured with the T25FW, using a responder analysis that assessed consistency of improvement during treatment. In another study,<sup>9</sup> we showed that consistent improvement provided a more sensitive criterion than an arbitrary threshold for average magnitude of change. Results from studies of fampridine in multiple sclerosis suggest that only some patients respond with clear clinical benefits on any particular functional measure. The selectivity of responsiveness might be related to the proposed mechanism of action—the improvement of conduction in demyelinated pathways via blockade of voltage-dependent potassium channels.<sup>1–3</sup> Only some patients would be expected to have axons susceptible to the drug effects at any given time.

Patients with faster walking speeds for most visits during study medication than the fastest speed during off-treatment period were defined as timed walk responders. The percentage of patients who met this criterion was 35% in the fampridine-treated group and

8% in the placebo group; this difference was both significant and very similar to the post-hoc results of the aforementioned phase II trial.<sup>9</sup> The degree of improvement—as measured by the average change in walking speed during the double-blind period—was about 25% for the fampridine-treated timed walk responders and 5% for the placebo group. The mean improvement in walking speed at every double-blind visit was greater in the fampridine-treated responder group than in the placebo group, showing maintenance of effect over 14 weeks of treatment. The average improvement in LEMMT score was also significantly greater in fampridine-treated timed walk responders than in patients on placebo.

Concerning clinical significance of the response criterion, timed walk responders reported significantly greater average improvement from baseline in the MSWS-12 score than non-responders. The two secondary validation measures, SGI and CGI, also showed significantly greater improvements in timed walk responders than in non-responders. In addition to this internal validation, walking speed is a useful and reliable clinical measure of impairment in multiple sclerosis.<sup>19,20</sup> The T25FW is a valid and reliable measure over time, shows negligible practice effects, and has moderate to strong correlation with EDSS.<sup>21–23</sup> Several investigators have concluded that a change in timed walk ability of 20% or more qualifies as a meaningful change.<sup>20,24–26</sup> Timed walk speed also correlates well with walking over longer distances and times.<sup>27–29</sup>

In our trial and in a preceding study,<sup>9</sup> no substantial difference was shown between fampridine-treated timed walk responders and non-responders in baseline demographics or multiple sclerosis symptoms, or any other available measure. The difference may be due to individual neuropathology. Interestingly, as in our phase II study, we observed here a transient improvement in walking speed in non-responders compared with that in the placebo group at the first visit after 2 weeks of treatment. This finding indicates that some non-responders differ from responders in their response to the drug over time.

The most frequent treatment-emergent adverse events in both treatment groups were common medical conditions affecting people with multiple sclerosis. Of those events arising in at least 5% of the fampridine-treated group, insomnia, fatigue, back pain, and balance disorder were each reported at rates more than 50% higher than those in the placebo group. This disparity could be a treatment-related increase. However, various adverse events seen in more than 5% of the placebo group were more than 50% more frequent than in the fampridine-treated group, including upper respiratory tract infection, increased blood concentrations of triglycerides, arthralgia, sinusitis, and blurred vision.

11 patients (5%) in the fampridine-treated group discontinued the study because of adverse events; eight

(4%) of these involved treatment-emergent events, and three were events that began before randomisation. Only two events were regarded by the investigator as at least possibly related to treatment: a focal seizure in a patient with sepsis and an episode of severe anxiety. This focal seizure was observed in the context of severe sepsis associated with community-acquired pneumonia. Risk of seizure seems to be increased in the multiple sclerosis population in general.<sup>30</sup> Although risk of seizure seems to increase in a dose-dependent way with fampridine and is consistent with its pharmacology, the frequency of seizures in clinical trials has been too low to show the presence of or estimate the magnitude of any increased risk at the current clinical dose of 10 mg twice daily.

More fampridine-treated than placebo patients showed a positive response of consistently improved walking speed, associated with an improvement in self-assessed ambulatory disability.

We provide evidence that treatment with fampridine produces clinically meaningful improvement in walking ability in some people with multiple sclerosis, irrespective of disease course type or concomitant treatment with immunomodulators. An additional phase III study is required to confirm these observations. Unlike the immunomodulator treatments for relapse prevention in multiple sclerosis, the efficacy of which can only be assessed in groups of patients, the effects of fampridine are rapid and reversible, which makes it possible to detect response in individuals. We could not identify any factor that predisposes patients with multiple sclerosis to respond to fampridine on a particular measure.

#### Contributors

ADG, RC, LNM, and ARB were involved in planning and design of the study. SRS participated in the assessment of study participants. ADG, TRB, SRS, RC, LNM, and ARB interpreted the data. ADG, TRB, LBK, RT, SRS, RC, LNM, and ARB drafted and critically revised the manuscript.

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#### Conflict of interest statement

ADG, TRB, and RTS were consultants to Acorda Therapeutics Inc. RC, LNM, and ARB were employed by and own stock in Acorda Therapeutics Inc. LBP and SRS declare that they have no conflict of interest.

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