Effects of Dalfampridine Extended-release Tablets on 6-minute Walk Distance in Patients With Multiple Sclerosis: A Post Hoc Analysis of a Double-blind, Placebo-controlled Trial

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ABSTRACT

Purpose: Dalfampridine extended-release (ER) tablets 10 mg BID have been approved for use in improving walking in people with multiple sclerosis (MS). This subgroup analysis evaluated the effects of dalfampridine ER 5 and 10 mg BID on distance walked, as assessed using the 6-minute walk (6MW) test.

Methods: This analysis of data from a randomized, placebo-controlled, double-blind study (N = 430) included only the 153 patients with 6MW data available. Participants (aged 18–70 years) were randomly assigned in a 1:1:1 ratio to receive dalfampridine ER 5 or 10 mg or placebo, BID for 4 weeks. The 6MW was used for assessing walking distance at baseline and 2 weeks after the start of treatment at the 26 study sites that were able to perform this test. Participants were administered the 12-item MS Walking Scale (MSWS-12), a patient-reported measure of the impact of MS on walking. Post hoc outcomes included the percentages of patients who achieved an increase from baseline in 6MW distance of ≥20% and who achieved a minimal clinically important difference (MCID) from baseline in 6MW distance, defined as ≥+55 m. Changes from baseline in walking speed (MSWS-12) were compared, stratified by subgroup that achieved ≥20% versus <20% improvement on the 6MW. The correlation between change in walking speed over time and subgroup (by change in distance walked) was evaluated. The tolerability of dalfampridine was assessed based on the prevalence of treatment-emergent adverse events (TEAEs).

Findings: In the post hoc analysis, the percentage of patients with an improvement in 6MW distance that met or exceeded the MCID was significantly greater with dalfampridine ER 10 mg BID relative to placebo (37.3% vs 12.2%; nominal $P = 0.004$). Similarly, the percentage with an improvement in 6MW distance of ≥20% was significantly greater with dalfampridine 10 mg BID relative to placebo (45.1% vs 14.3%; nominal $P < 0.001$). Regardless of treatment allocation, improvement in MSWS-12 was significantly greater in the subgroup that achieved a ≥20% improvement on the 6MW compared with the subgroup with <20% improvement (mean changes, –15.5 vs –7.2; nominal $P = 0.041$). The prevalences and types of TEAEs were consistent with those reported in previous studies.

Implications: Based on the MCID for 6MW, the use of dalfampridine ER 10 mg BID but not 5 mg BID was associated with statistically significant and clinically meaningful improvements in walking relative to placebo. The correlation between improvement on

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MSWS-12 and the 20% increase in 6MW distance suggests that an improvement on MSWS-12 is clinically relevant. These results, although highlighting a lack of efficacy of dalfampridine ER 5 mg BID, suggest that the 10-mg BID dose is effective for improving walking speed, as observed on short timed-walk tests, and for increasing distance walked over longer timed-walk periods. ClinicalTrials.gov identifier: NCT01328379. (*Clin Ther*. 2015;37:2780–2787)

Key words: 4-aminopyridine, 6-minute walk test, ambulation, dalfampridine, multiple sclerosis, subgroup analysis.

INTRODUCTION

Mobility impairment is common among patients with multiple sclerosis (MS). Thus, it may not be surprising that 70% of people with MS consider walking difficulty as the most challenging aspect of the disease.[1] Based on consistent changes in walking speed in 2 pivotal studies,[2,3] the use of dalfampridine extended-release (ER) tablets (also known as prolonged-release fampridine in Europe and as fampridine modified- or sustained-release elsewhere) 10 mg BID for improving walking in people with MS has been approved by the US Food and Drug Administration.[4] Dalfampridine ER is a broad-spectrum inhibitor of voltage-gated potassium channels, with a putative mechanism of action of improving action-potential conduction in the demyelinated axons that are characteristic of MS.[5]

To fulfill a postmarketing regulatory commitment, a study was performed to evaluate the efficacy and safety profile of dalfampridine ER 5 mg BID, relative to the approved dose of 10 mg BID, to those of placebo was performed.[6] The primary efficacy end point of the original study, change from baseline on the timed 25-foot walk (T25FW) test at 4 weeks after the start of treatment, was not significantly different between either of the active treatment groups and the placebo group. However, in a post hoc analysis of mean data from all study visits, walking speed was significantly increased in the 10-mg BID dose group compared with that in the placebo group (nominal $P = 0.014$).[6] Additionally, in a subgroup analysis, the change from baseline in walking distance, as assessed using the 6-minute walk (6MW) test,[7] was a prespecified secondary end point. A significant improvement in 6MW distance occurred in the 10-mg BID dose group, but not in the 5-mg BID dose group, versus the placebo group (nominal P values, 0.014 and 0.308, respectively).

In this report, we expand on the results obtained using the 6MW, further evaluate the effects of dalfampridine ER 5 and 10 mg BID on walking distance, and explore the relationship between these objective assessments and patient-reported walking outcomes.

PATIENTS AND METHODS

Study Design

A detailed description of the patient selection and methodology in this study has been previously published.[6] In brief, in this randomized, double-blind, placebo-controlled, parallel-group study, after a 1-week screening period, participants were randomly assigned, in a 1:1:1 ratio, to receive dalfampridine ER 5 or 10 mg or placebo, BID for 4 weeks. The study was performed in accordance with the revised Declaration of Helsinki. The protocol was approved by the appropriate institutional review boards or independent ethics committees, and all patients provided written informed consent.

Eligible participants were 18 to 70 years of age, had been diagnosed with MS, and had MS-related walking impairment but with ambulatory ability sufficient for completing the T25FW. A washout period of at least 4 weeks before screening was required in participants who had previously been taking dalfampridine.

Efficacy Assessments

The study was performed at 65 sites in the United States, of which 26 were appropriate for administering the 6MW, which was used for assessing walking distance at baseline and at 2 weeks after the start of treatment. The 6MW was performed on a 30.48-m (100-ft) walkway, with the starting line and turn-around points clearly marked, and participants were instructed to walk as far and as fast as possible, back and forth, for 6 minutes, without rest or encouragement.[7] The 6MW and the T25FW were administered by an evaluator blinded to other clinical and safety data on each patient, including each patient's self-report on the 12-item Multiple Sclerosis Walking Scale (MSWS-12).[8]

Before the administration of the 6MW, participants were administered the MSWS-12,[8] a multi-item scale that enables patients to self-rate the impact of MS on their walking during the preceding 2 weeks. It assesses a range of walking-related functions and addresses the quality of walking as well as the need for assistive devices.[8] Responses on the MSWS-12 are ratings on a 5-point Likert-type scale (from 1 = not at all to 5 = extremely), and the scores are transformed to a range of 0 to 100, with greater scores indicating greater impact on walking.

Tolerability Assessment

Safety profile and tolerability measures included the prevalences of treatment-emergent adverse events (TEAEs), vital sign measurements, clinical laboratory tests, and electrocardiography.

Statistical Analysis

A sample size of 135 patients per group was calculated as being needed for ~90% power to detect a difference of 0.16 ft/sec in the primary efficacy end point (T25FW) between dalfampridine ER 10 mg BID and placebo. This determination was based on previously observed differences between dalfampridine ER 10 mg BID and placebo and used an assumed SD of 0.40 ft/sec[2,3].

Data from patients with data from 6MW assessments available from baseline and week 2 of treatment were included in this analysis. Treatment effects (6MW) were compared using ANOVA, with terms for treatment and baseline for the prespecified secondary end point. Two types of post hoc responder analyses were used for addressing the potential clinical meaningfulness of change in 6MW distance. A change in walking distance of 55.06 m (95% CI, 30.62–79.51) (180.64 ft [95% CI, 100.46–260.86]) on the 6MW was previously estimated as the minimal clinically important difference (MCID), using the Expanded Disability Status Scale score as an anchor.[9] The initial analysis of response was performed using this criterion, although it may be considered potentially inappropriate to apply across a wide range of walking deficits; the baseline walking distances in the individuals in this study ranged from 23.8 to 521.2 m, with a mean of 259.0 m. The criterion of a +55.06-m change would therefore represent an improvement of 21.3% in the average patient, but would be a 231.3% improvement in the slowest patient and 10.6% in the fastest. Based on previous work indicating that a 20% improvement on the T25FW was clinically meaningful,[10] the same criterion was adopted for the second post hoc analysis of response. Thus, the percentages of patients who achieved an improvement of ≥55.06 m, and the percentages who achieved a ≥20% improvement, on the 6MW at 2 weeks relative to baseline were determined and compared across treatments using the Cochran-Mantel-Haenszel test.

To examine further the clinical relevance of the 20% threshold, the changes from baseline in MSWS-12 score were compared between the subgroup that showed a ≥20% improvement on the 6MW versus the subgroup with <20% improvement, using ANOVA. Because earlier studies reported that results on the 6MW were strongly correlated with results from assessments of ambulatory dysfunction in MS, including the T25FW,[7,11,12] an additional post hoc analysis was performed to determine whether change in walking speed over time is correlated with change in distance walked. These correlations were assessed using Pearson correlation coefficients.

RESULTS

Patients

The baseline characteristics and disposition of the patients who completed the 6MW are shown in Table I and Figure 1, respectively. Demographic and clinical characteristics at baseline were similar among the treatment groups. Across groups, the mean age varied from 52.0 to 53.9 years. The distribution of Expanded Disability Status Scale scores was 5.0 to 5.1, which was comparable to that in the full study population (4.7–4.8).[6] At baseline, the mean 6MW distance across groups ranged from 256.5 to 262.4 m (841.5–860.9 ft).

Efficacy

The mean change from baseline in 6MW distance at 2 weeks of treatment was significantly greater with the 10-mg BID dose (+39.2 m [+128.6 ft]), but not with the 5-mg BID dose (+23.4 m [+76.8 ft]), compared with placebo (+12.7 m [+41.7 ft]; nominal *P* values, 0.014 and 0.308, respectively).[6] On post hoc analysis of the 6MW distance, the percentages of patients who had improvements that met or exceeded the estimated MCID relative to placebo were 26.4% and 37.3% with the 5- and 10-mg BID

Table I. Baseline demographic and clinical characteristics of the patients who completed the 6MW.

Variable	Dalfampridine ER 5 mg BID (n = 53)	Dalfampridine ER 10 mg BID (n = 51)	Placebo (n = 49)	P
Age, mean (SD), y	52.0 (9.6)	53.9 (9.3)	53.8 (8.9)	0.510
Female, no. (%)	45 (84.9)	35 (68.6)	37 (75.5)	0.147
Race, no. (%)				0.053
White	38 (71.7)	44 (86.3)	40 (81.6)	
Black/African American	15 (28.3)	5 (9.8)	9 (18.4)	
Other	0	2 (3.9)	0	
EDSS score, mean (SD)	5.0 (1.5)	5.0 (1.4)	5.1 (1.5)	0.976
Walking speed (T25FW), ft/sec				0.728
Mean (SD)	2.63 (0.91)	2.81 (1.07)	2.73 (1.41)	
Median (range)	2.6 (0.6–5.2)	2.8 (0.8–5.1)	2.5 (0.4–6.2)	
6MW distance, ft				0.956
Mean (SD)	841.5 (328.5)	842.6 (322.9)	860.9 (428.6)	
Median (range)	864.0 (174.0–1700.0)	900.0 (78.0–1510.0)	794.0 (100.0–1710.0)	
MSWS-12 score				0.182
Mean (SD)	66.0 (21.2)	57.7 (27.8)	64.7 (24.2)	
Median (range)	68.8 (12.5–100.0)	58.3 (0.0–97.9)	72.9 (8.3–97.9)	

6MW = 6-min walk test; EDSS = Expanded Disability Status Scale; ER = extended release; MSWS-12 = 12-item Multiple Sclerosis Walking Scale; T25FW = timed 25-ft walk test.

doses, respectively, versus 12.2% with placebo (Figure 2), with a dose response apparent in the 10-mg BID dose group only (nominal $P = 0.004$). Additionally, the percentages of patients who achieved a ≥20% increase in 6MW distance were 28.3% and 45.1% with dalfampridine ER 5 and 10 mg BID relative to placebo (14.3%) (Figure 2), with only the 10-mg BID dose showing significance compared with placebo (nominal $P < 0.001$).

Regardless of treatment allocation, the subgroup that achieved a ≥20% increase in 6MW distance was observed to have had a significantly greater improvement in mean MSWS-12 score compared with the subgroup that had <20% improvement in walking distance (mean change, −15.5 vs −7.2; nominal $P = 0.041$) (Figure 3).

The change from baseline in 6MW distance was correlated with change on the T25FW across treatment groups (Table II), although the strength of the correlation varied to some extent with the magnitude of change observed in each treatment group.

Safety Profile

A total of 58.8% of the participants with 6MW data experienced ≥1 TEAE, with a similar overall prevalence among all 3 treatment groups (Table III). The most commonly reported treatment-related TEAEs across all treatment groups included headache, dizziness, nausea, insomnia, and urinary tract infection, but no clear patterns were observed in this subpopulation. There were no clinically meaningful changes in vital sign measurements or on electrocardiography by treatment group.

DISCUSSION

Previously, we reported that treatment with dalfampridine ER 10 mg BID, but not 5 mg BID, was associated with increased walking distance on the 6MW relative to placebo (39.2 m [128.6 ft] vs 12.7 m [41.7 ft]; nominal $P = 0.014$).[6] This effect was seen in the subset of patients evaluated with this test despite the fact that the primary efficacy end point of the study, a single time-point assessment of change

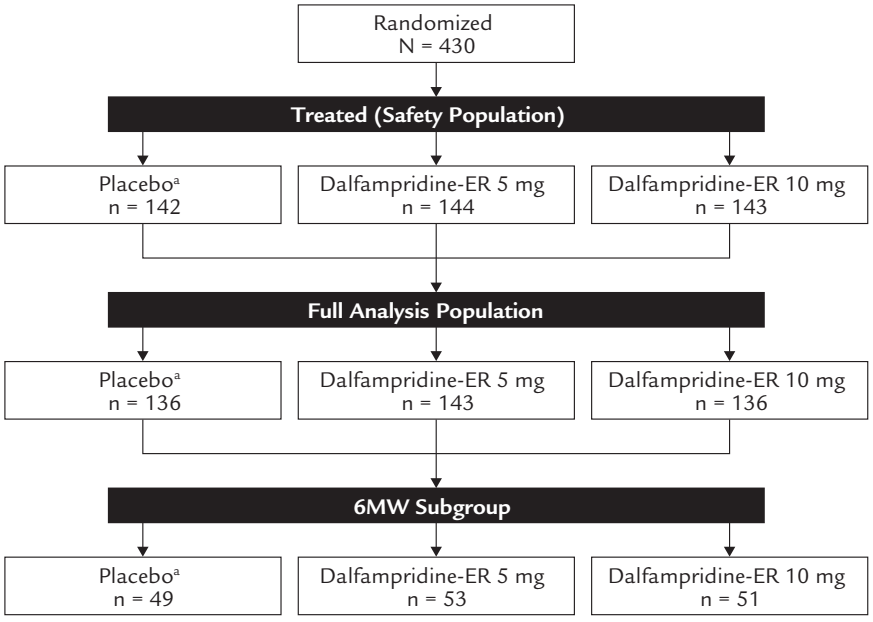

Figure 1. Patient disposition showing subgroup-analysis population of patients who completed the 6-minute walk (6MW) test after treatment with dalfampridine extended release (ER) or placebo. [a]One patient was randomized but did not receive treatment. Results from the full analysis population were reported by Yapundich et al.[6]

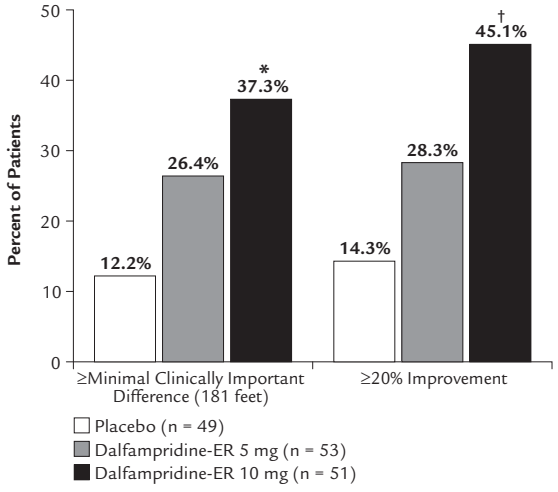

Figure 2. Rates of achievement of improvement thresholds on the 6-minute walk (6MW) test after 2 weeks of treatment with dalfampridine extended release (ER) or placebo. $^{*}P = 0.004$ and $^{\dagger}P < 0.001$ versus placebo.

from baseline in walking speed on the T25FW, did not reach statistical significance with either dose of dalfampridine ER relative to placebo. These findings suggest that longer walking tests, such as the 6MW, may be more sensitive for detecting the treatment effects of dalfampridine ER, although further evaluation over a longer treatment duration is needed for determining the long-term effects of dalfampridine ER on walking distance.

Expanding on our previous primary results,[6] we report that 45% of the patients treated with dalfampridine ER 10 mg BID had an increase in distance walked of ≥20% relative to baseline, and that 37% of patients had an increase in walking distance relative to baseline that met or exceeded the previously estimated MCID of 55.06 m (180.64 ft). In contrast, among patients treated with dalfampridine ER 5 mg BID, only 28% had an increase in walking distance of ≥20%, and in 26%, the MCID was exceeded. These findings corroborate our previous conclusion that the approved dose, 10 mg BID, is the minimal dose effective for improving walking in patients with MS.[6] The safety profile in this

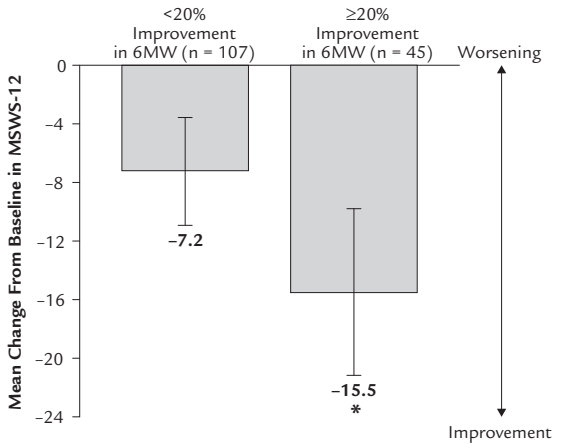

Figure 3. Associations between mean (95% CI) changes from baseline in patient-perceived improvements in walking, as measured using the 12-item Multiple Sclerosis Walking Scale (MSWS-12), and thresholds of improvement on the 6-minute walk (6MW) test, after 2 weeks of treatment with dalfampridine extended release (ER) or placebo. *$P = 0.041$ versus subgroup with <20% improvement in 6MW (ANOVA).

subpopulation was consistent with that reported in the full study population.[6]

Although a 20% change in walking speed, as measured using the T25FW, has been supported by the findings from a number of studies as being clinically meaningful,[10] the clinical relevance of a ≥20% improvement on the 6MW has not been established in patients with MS. However, in this study, the mean change in MSWS-12 score in the subgroup of patients with ≥20% improvement on the 6MW was –15.5 compared with –7.2 in the subgroup with <20% improvement, suggesting that this threshold may be clinically relevant because patients perceive that such a change has an impact on their walking ability. These results parallel the observations in the full analysis population (N = 415), in which a ≥20% increase in average walking speed on the T25FW was associated with a similar improvement in mean MSWS-12 scores (–15.8) compared with <20% improvement (–6.6).[6] Additionally, the estimated 55.06 m MCID represented 21.6% of the mean baseline distance in this substudy. This consistency across analyses supports the concept that a ≥20% improvement in 6MW distance likely reflects a clinically meaningful change.

An important limitation of this study was that it was performed in a subpopulation; because the 6MW

Table II. Associations between changes from baseline in walking distance and walking speed in patients who completed the 6MW after 2 weeks of treatment with dalfampridine or placebo.

	Dalfampridine ER		
Parameter	5 mg BID (n = 53)	10 mg BID (n = 51)	Placebo (n = 49)
Change in 6MW, ft			
Mean (SD)	+76.8 (198.8)	+128.6 (154.7)	+41.7 (163.5)
Median (range)	+67 (–620 to +670)	+150 (–190 to +472)	+40 (–383 to +600)
Change in T25FW, ft/sec			
Mean (SD)	0.33 (0.50)	0.36 (0.46)	0.18 (0.51)
Median (range)	0.28 (–0.53 to +2.03)	0.33 (–0.45 to +1.45)	0.19 (–1.12to +1.97)
T25FW vs 6MW, correlation coefficient	0.62 ($P < 0.0001$)	0.64 ($P < 0.0001$)	0.47 ($P = 0.0007$)

6MW = 6-min walk test; ER = extended release; T25FW = timed 25-ft walk test.

Table III. Tolerability of 4 weeks of treatment with dalfampridine. Data are given as number (%) of patients.

Parameter	Dalfampridine ER 5 mg BID (n = 53)	Dalfampridine ER 10 mg BID (n = 51)	Placebo (n = 49)
Any TEAE	32 (60.4)	30 (58.8)	28 (57.1)
Most common* TEAEs			
Headache	7 (13.2)	7 (13.7)	5 (10.2)
Nausea	7 (13.2)	5 (9.8)	2 (4.1)
Insomnia	4 (7.5)	5 (9.8)	2 (4.1)
Fall	4 (7.5)	1 (2.0)	3 (6.1)
Dizziness	3 (5.7)	5 (9.8)	2 (4.1)
Dyspepsia	3 (5.7)	–	1 (2.0)
Pain	3 (5.7)	–	1 (2.0)
Paresthesia	2 (3.8)	4 (7.8)	2 (4.1)
Urinary tract infection	2 (3.8)	3 (5.9)	2 (4.1)
Balance disorder	2 (3.8)	2 (3.9)	3 (6.1)
Nasopharyngitis	1 (1.9)	3 (5.9)	–
Pain in extremity	–	5 (9.8)	–
Dry mouth	–	3 (5.9)	–

ER = extended release; TEAE = treatment-emergent adverse event.
*Prevalence of ≥5% in any treatment group, by Medical Dictionary for Regulatory Activities preferred term.

protocol requires a 100-ft hallway, only a subset of study sites were appropriate for administering the test. Despite this limitation, in this post hoc analysis, the percentage of patients who achieved improvement in walking distance was significantly greater in the group treated with dalfampridine ER 10 mg BID relative to placebo, and more than one third of the patients achieved the estimated MCID of 55.06 m (180.64 ft). However, that MCID was estimated in a population that had an overall level of disability that was lesser than that in the current study, and the MCID was for deterioration of walking ability; it is not clear whether the MCID would also apply to an improvement in walking distance. A threshold of the percentage change in walking distance may be more clinically meaningful than an absolute MCID value in distance because a percentage increase can represent a clinically relevant change across a broader range of baseline values based on disability level. The findings with regard to MSWS-12 further support a 20% threshold; regardless of treatment allocation, the subgroup with a ≥20% improvement in walking distance had a significantly greater improvement on the MSWS-12 compared with that in the subgroup that had a <20% improvement on the 6MW. Although the percentage of patients whose 6MW was improved by ≥20% was numerically greater with dalfampridine ER 5 mg BID relative to placebo, the difference was not statistically significant, supporting the appropriateness of 10-mg-BID dosing for improvement in walking in patients with MS.

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CONFLICTS OF INTEREST

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