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Safety and Efficacy of 5 mg and 10 mg Dalfampridine Extended Release Tablets in Patients with Multiple Sclerosis: First Results from a Double-Blind, Placebo-Controlled Trial

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Background

- Dalfampridine extended release tablets (dalfampridine-ER; known as prolonged-release fampridine in Europe and as fampridine modified or sustained release elsewhere), 10 mg twice daily, are available in the United States to improve walking in people with multiple sclerosis (MS)[1] based on a consistent response criterion[2,3]
- Dalfampridine-ER was observed to have a favorable tolerability profile at the recommended therapeutic dose and regimen in clinical trials, and postmarketing safety data suggest a similar profile in clinical practice[2]
- To fulfill an FDA-required post-marketing commitment, a lower, 5-mg dose of dalfampridine was tested for efficacy and tolerability using a previously untried single endpoint analysis

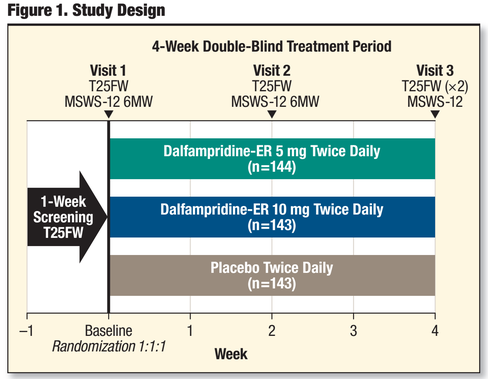
Objective

- To evaluate the efficacy and tolerability of dalfampridine-ER tablets at a dose strength of 5 mg twice daily compared with the approved dose of 10 mg twice daily for improving walking in patients with MS

Methods

- This study was performed in accordance with the revised Declaration of Helsinki; approval was obtained from the appropriate institutional review boards or independent ethics committees, and all patients provided written informed consent
- This was a randomized, placebo-controlled, double-blind, 3-arm, parallel group study (**Figure 1**)

Figure 1. Study Design



ER, extended release; MSWS-12, 12-item Multiple Sclerosis Walking Scale; 6MW, 6-Minute Walk Test; T25FW, Timed 25-Foot Walk Test.

- After a 1-week screening period, subjects meeting all inclusion and exclusion criteria (**Table 1**) were randomized to treatment with either twice daily dalfampridine-ER 5 mg (n=144), 10 mg (n=143), or placebo (n=143) for 4 weeks

Table 1. Key Eligibility Criteria

Inclusion	Exclusion
• Diagnosis of clinically definite MS defined by the 2005 revision of the McDonald Criteria[3]	• Women who are pregnant or breastfeeding
• Age 18 to 70 years of age, inclusive	• History of seizures
• Women of childbearing potential must have a negative urine pregnancy test at the Screening Visit and consent to use of adequate contraception for the study duration	• Presence or history of moderate or severe renal impairment defined by a calculated creatinine clearance ≤50 mL/minute
• Presence of an MS-related walking impairment but with sufficient ambulatory ability to be able to complete all evaluations of the T25FW	• Presence of an active urinary tract infection at Screening or within the 4 weeks before Screening
• Patients who have taken any formulation of dalfampridine-ER must have withdrawn from the drug for at least 1 month prior to Screening	• An onset of an MS exacerbation within 60 days prior to Screening

ER, extended release; MS, multiple sclerosis; T25FW, Timed 25-Foot Walk Test.

- Efficacy and tolerability assessments were performed at all study visits: at randomization (Visit 1), at 2 weeks after treatment initiation (Visit 2), and at end of treatment (Visit 3)
- Unlike the registration trials' consistent response criterion,[2,3] the primary efficacy endpoint was the previously untested change from baseline in walking speed (WS) using the Timed 25-Foot Walk Test (T25FW) at 3–4 hours after the last dose of dalfampridine-ER at Week 4
  - This time point approximates the peak dalfampridine-ER plasma concentration at steady state (C_{maxSS})[4]
- Treatment effects were compared using analysis of variance (ANOVA)
  - Evaluation was based on the full analysis population, defined as all randomized patients who took at least 1 dose of double-blind treatment and who had a baseline and at least 1 post-baseline T25FW assessment
- Distance walked was also evaluated using the 6 Minute Walk (6MW) test as a pre-specified analysis in the subset of study sites (n=26) that had the capability for performing this test
  - The 6MW was performed in a 100-foot hallway with starting line and turnaround points clearly marked, and patients were instructed to walk as far and as fast as possible back and forth in the hallway for 6 minutes without rest or encouragement[5]
  - Treatment effects, measured as change from baseline at Visit 2, were compared using an ANOVA model
- Tolerability was evaluated based on the incidence of adverse events (AEs) during the double-blind treatment period
- A *post hoc* analysis compared change from baseline in WS between dalfampridine-ER and placebo by combining the two T25FW assessments prior to treatment as the baseline (Screening and Visit 1) and the three on-treatment T25FW assessments as the on-drug value (Visits 2 and 3)
  - This analysis was similar to those previously evaluated in clinical trials[6,7]

Results

- Demographic and clinical characteristics were balanced among treatment groups (**Table 1**)
  - Subjects were primarily women (70%), and the mean age was 52.6 years
  - The main diagnosis type was relapsing-remitting MS (73.2%), and overall mean baseline WS was 2.75 ft/sec

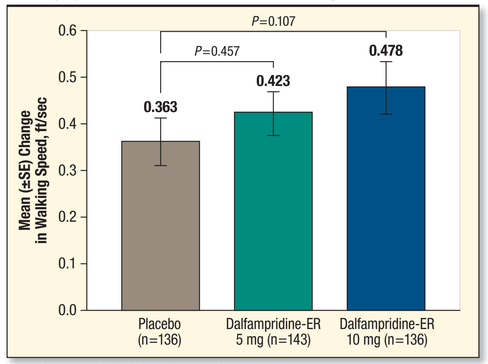
Table 2. Demographic and Clinical Characteristics of the Treatment Groups at Baseline

Variable		Placebo* (n=142)	Dalfampridine-ER 5 mg (n=144)	Dalfampridine-ER 10 mg (n=143)
Gender, n (%)	Male	42 (29.6)	42 (29.2)	45 (31.5)
	Female	100 (70.4)	102 (70.8)	98 (68.5)
Age, years, mean±SD		52.2±9.9	52.2±9.3	53.4±9.5
Race, n (%)	Asian	1 (0.7)	1 (0.7)	1 (0.7)
	White	117 (82.4)	113 (78.5)	114 (79.7)
	African American	22 (15.5)	27 (18.8)	24 (16.8)
	Other	2 (1.4)	3 (2.1)	4 (2.8)
BMI, kg/m², mean±SD		28.3±7.1	28.3±6.6	29.1±5.8
MS diagnosis type, n (%)				
Relapsing-remitting		103 (72.5)	104 (72.2)	107 (74.8)
Secondary-progressive		23 (16.2)	19 (13.2)	21 (14.7)
Primary-progressive		12 (8.5)	17 (11.8)	11 (7.7)
Progressive-relapsing		4 (2.8)	4 (2.8)	4 (2.8)
Disease duration, years, mean±SD		13.0±9.5	11.3±8.5	12.1±9.0
EDSS score, mean±SD		4.8±1.6	4.8±1.5	4.7±1.5
Walking speed, ft/sec, mean±SD		2.78±1.16	2.65±1.02	2.84±1.21

*One patient was randomized to the placebo group, but did not take any doses.
BMI, body mass index; EDSS, Expanded Disability Status Scale; ER, extended release; MS, multiple sclerosis; SD, standard deviation.

- A total of 31 patients withdrew from the study including 10 (7.0%) in the placebo group, 6 (4.2%) in the dalfampridine-ER 5-mg group, and 15 (10.5%) in the dalfampridine-ER 10-mg group
  - The most common reason for discontinuation was AEs, occurring in 5 (3.5%), 3 (2.1%), and 14 (9.8%) patients in the placebo, dalfampridine-ER 5-mg, and 10-mg groups, respectively
  - Other reasons included non-compliance (n=3; 0.7%), lost to follow-up (n=2; 0.5%), investigator decision (n=1; 0.2%) and other (n=2; 0.5%)
- There was no statistically significant difference with placebo with either dalfampridine-ER 5 mg ($P=0.457$) or 10 mg ($P=0.107$) as measured by the T25FW in a single point analysis (**Figure 2**)

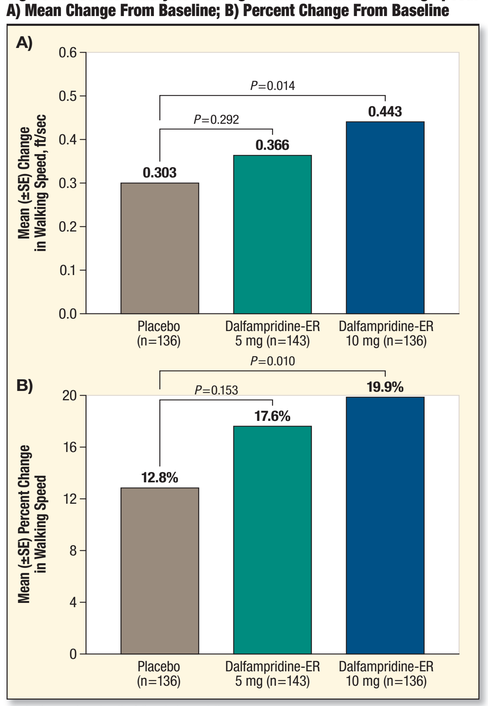
Figure 2. Primary Efficacy Endpoint*: Change From Baseline in Walking Speed at Visit 3 at 3–4 Hours Following the Last Dose†



*Evaluation was based on the full analysis population.
†Approximately corresponding to peak plasma concentration (C_{maxSS}) of dalfampridine.
ER, extended release; SE, standard error.

- In the *post hoc* analysis, which used measures similar to those previously evaluated in clinical trials,[6,7] the change from baseline in WS for dalfampridine-ER 10 mg (0.443 ft/sec) was significantly greater than the change with placebo (0.303; $P=0.014$) (**Figure 3A**)

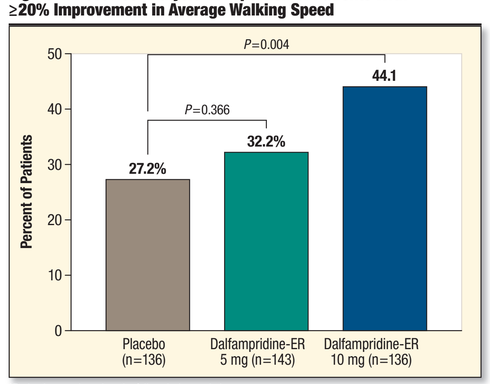
Figure 3. *Post Hoc* Analysis*: Change From Baseline in Walking Speed. A) Mean Change From Baseline; B) Percent Change From Baseline



*Evaluation was based on the full analysis population.
ER, extended release; SE, standard error.

- The difference between dalfampridine-ER 5 mg and placebo was not significant ($P=0.292$)
- Similarly, the mean percent change in WS from baseline was significantly greater than placebo for dalfampridine-ER 10 mg (19.9% versus 12.8%; $P=0.010$), but not for dalfampridine-ER 5 mg (**Figure 3B**)
- Using a response analysis of average improvement in WS ≥20% from baseline, there were significantly more responders with dalfampridine-ER 10 mg relative to placebo (44.1% versus 27.2%; $P=0.004$), but not with dalfampridine-ER 5 mg (**Figure 4**)
  - This response analysis is similar to that presented graphically in the dalfampridine-ER prescribing information[1]

Figure 4. *Post Hoc* Analysis*: Proportion of Patients With ≥20% Improvement in Average Walking Speed



*Evaluation was based on the full analysis population.

- Significant improvement in walking distance was observed relative to placebo with the dalfampridine-ER 10-mg dose, but not the 5-mg dose (**Table 3**)
  - The 2-week change from baseline with dalfampridine-ER 10 mg was approximately 3 times greater than that of placebo (128.6 feet versus 41.7 feet; $P=0.014$)

Table 3. Change from Baseline in Walking Distance at 2 Weeks, Assessed Using the 6MW

Treatment Group	Mean (±SE) Change from Baseline, Feet	*P*-value versus Placebo
Placebo (n=49)	41.7±23.4	—
Dalfampridine-ER 5 mg (n=53)	76.8±27.3	0.308
Dalfampridine-ER 10 mg (n=51)	128.6±21.7	0.014

ER, extended release; SE, standard error; 6MW, 6-Minute Walk Test.

- A more complete analysis of the 6MW has been presented as an oral presentation (S01.007, Tuesday, March 19, 2013, American Academy of Neurology)
- The overall incidence of treatment-emergent adverse events (TEAEs) was generally similar among the treatment groups (**Table 4**)
  - TEAEs were generally mild or moderate in severity
- No seizures were observed and there were no deaths
- Six serious AEs occurred in 4 patients including breast abscess with associated cellulitis, and urosepsis in the dalfampridine-ER 5-mg group; ovarian adenoma, vertigo, and a loss of consciousness (4 days after drug discontinuation) in the dalfampridine-ER 10-mg group
  - The urosepsis, vertigo, and loss of consciousness were deemed by the Investigator to be treatment related

Table 4. Summary of Treatment-Emergent Adverse Events (TEAEs)

Adverse Event, n (%)	Placebo (n=143)	Dalfampridine-ER 5 mg (n=144)	Dalfampridine-ER 10 mg (n=142)	Dalfampridine-ER All (n=286)
Any TEAE	77 (53.8)	80 (55.6)	84 (59.2)	164 (57.3)
Treatment-related TEAEs	27 (18.9)	32 (22.2)	40 (28.2)	72 (25.2)
TEAEs by maximum severity				
Mild	37 (25.9)	45 (31.3)	41 (28.9)	86 (30.1)
Moderate	28 (19.6)	27 (18.8)	33 (23.2)	60 (21.0)
Severe	12 (8.4)	8 (5.6)	10 (7.0)	18 (6.3)
TEAEs leading to withdrawal	5 (3.5)	3 (2.1)	14 (9.9)	17 (5.9)
Serious TEAEs	0	2 (1.4)	2 (1.4)	4 (1.4)
Deaths	0	0	0	0
Most common treatment-related TEAEs*				
Diarrhea	3 (2.1)	0	1 (0.7)	1 (0.3)
Dyspepsia	1 (0.7)	4 (2.8)	0	4 (1.4)
Nausea	3 (2.1)	4 (2.8)	8 (5.6)	12 (4.2)
Urinary tract infection†	3 (2.1)	4 (2.8)	5 (3.5)	9 (3.1)
Decreased appetite	1 (0.7)	0	3 (2.1)	3 (1.0)
Pain in extremity	2 (1.4)	0	3 (2.1)	3 (1.0)
Balance disorder	4 (2.8)	2 (1.4)	1 (0.7)	3 (1.0)
Dizziness	2 (1.4)	5 (3.5)	11 (7.7)	16 (5.6)
Headache	7 (4.9)	6 (4.2)	9 (6.3)	15 (5.2)
Paraesthesia	1 (0.7)	1 (0.7)	5 (3.5)	6 (2.1)
Insomnia	3 (2.1)	7 (4.9)	9 (6.3)	16 (5.6)

*Occurring in ≥ 2 patients for preferred term; †reported as symptomatic urinary tract infections.

- The most common AEs leading to withdrawal were those related to gastrointestinal disorders and musculoskeletal disorders, and were more frequent with dalfampridine-ER
- The most common treatment-related TEAEs were consistent with previous studies[6,7]
  - Among dalfampridine-treated patients, dizziness, insomnia, and nausea were the most frequent treatment-related TEAEs

Conclusions

- Dalfampridine-ER 5 mg twice daily failed to demonstrate efficacy in the improvement of walking
- While the 10-mg dose did not show statistically significant effects using a previously untested outcome measure, significant effects were observed in a *post hoc* analysis using measures similar to those in clinical studies and described in the prescribing information
- The 10-mg dose, but not the 5-mg dose, showed a significant improvement compared with placebo on the 6MW
- The tolerability profile was consistent with previous reports
- Based on the findings from this study, 10 mg twice daily appears to be the minimally effective dose for improvement of walking

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